

# **Prospective observational study assessing the impact of elafibranor on fatigue, work productivity/activity impairment, and pruritus in patients with PBC**

## **STUDY PROTOCOL STUDY NUMBER: CLIN-60190-477 [IPN60190]**

Final V1.0: 17 July 2026

### **Sponsor**

Ipsen Biopharmaceuticals Inc.  
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Cambridge, MA 02142

Tel: PPD

**PROTOCOL SIGNATURES****Investigator Signature:**

I have read and agree to the CLIN-60190-477 - Prospective observational study assessing the impact of elafibranor on fatigue, work productivity/activity impairment, and pruritus in patients with PBC. I am aware of my responsibilities as an Investigator under the guidelines of Good Pharmacoepidemiology Practices, Good Pharmacovigilance Practices, any regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: \_\_\_\_\_

TITLE: Principal Investigator: PPD SIGNATURE: \_\_\_\_\_

PPD

DATE: \_\_\_\_\_

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DATE: \_\_\_\_\_

Full study site contact details, including telephone numbers, will be documented in the Study Master File.

**On behalf of the Sponsor:**

NAME: PPD

TITLE: SIGNATURE: \_\_\_\_\_

DATE: \_\_\_\_\_

## SYNOPSIS

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| <b>Study Title:</b>      | Prospective observational study assessing the impact of elafibranor on fatigue, work productivity/activity impairment, and pruritus in patients with PBC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Study Objectives:</b> | <p><u>Primary objective</u></p> <ul style="list-style-type: none"> <li>To evaluate participant-reported fatigue at baseline (pre-initiation of elafibranor) and through Month 3, Month 6, and Month 12 (M3, M6, and M12) after initiation of elafibranor for treatment of PBC (reference date).</li> </ul> <p><u>Secondary objectives</u></p> <ul style="list-style-type: none"> <li>To describe the demographic and baseline clinical characteristics of participants at the reference date.</li> <li>To evaluate participant-reported work productivity and activity impairment at baseline and through M3, M6, and M12 after the reference date.</li> <li>To evaluate PBC-40 domains other than Fatigue at baseline and through M3, M6, and M12 after the reference date.</li> <li>To evaluate itch severity using the WI-NRS at baseline and through M3, M6, and M12 after the reference date.</li> </ul> <p><u>Exploratory Objectives</u></p> <ul style="list-style-type: none"> <li>To describe liver function parameters (alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin) at baseline and through M3, M6, and M12 after the reference date.</li> <li>To explore the association between liver function parameters (ALP, ALT, AST and bilirubin) and reported fatigue levels at baseline and through M3, M6, and M12 after the reference date.</li> <li>To explore the association between fatigue scores and other PBC-40 domain scores at baseline and through M3, M6, and M12 after the reference date.</li> <li>To explore the association between fatigue scores and WPAI-SHP domain scores at baseline and through M3, M6, and M12 after the reference date.</li> <li>To characterize WPAI-SHP domain scores in participants at baseline and through M3, M6, and M12 after the reference date, stratified by age and clinical severity.</li> </ul> |
| <b>Rationale</b>         | Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune liver disease that is characterized by the gradual destruction of small intrahepatic bile ducts, leading to cholestasis, liver inflammation, and, if untreated, progression to cirrhosis. The disease is associated with characteristic biochemical abnormalities, including elevations in ALP, ALT, AST, and bilirubin, which reflect                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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|  | <p>cholestasis and hepatocellular injury. PBC predominantly affects women and is most commonly diagnosed in middle adulthood.</p> <p>In addition to progressive liver injury, PBC is associated with a substantial symptom burden. Fatigue affects up to 80% of participants with PBC, with approximately 20% experiencing severe, persistent fatigue that significantly impairs quality of life. Pruritus is reported in 50%–81% of participants, with about 30% experiencing clinically significant symptoms. These symptoms are often poorly correlated with conventional markers of liver disease severity and can occur even in early stages of PBC.</p> <p>Fatigue and pruritus can substantially impair health related quality of life (HRQoL); further, pruritus can disrupt sleep, and both fatigue and pruritus can limit daily functioning and work productivity, negatively affecting emotional well-being. Anecdotal reports indicate that fatigue is historically underreported, in part due to the lack of effective treatments, underscoring the need for therapies and supportive strategies that specifically target this participant-reported burden.</p> <p>Ursodeoxycholic acid (UDCA) is the first-line therapy for PBC. While effective as a treatment to slow disease progression for many participants, it does not result in a sufficient biochemical response in up to 40% of participants. For those with an inadequate response or intolerance to UDCA, second-line therapies include elafibranor and seladelpar, both approved by the FDA in 2024. These agents act as PPAR agonists and have demonstrated improvements in biochemical markers and symptoms.</p> <p>In the pivotal Phase 3 ELATIVE trial, elafibranor demonstrated significant improvements in biochemical response compared with placebo. Improvements in pruritus were observed as measured by the PBC-40 itch domain and the 5-D Itch scale after 52 weeks of treatment. Post hoc analyses suggested improvements in fatigue measures, including PROMIS Fatigue–Short Form 7a and the PBC-40 fatigue domain, particularly among participants with moderate-to-severe fatigue at baseline.</p> <p>While clinical trials have demonstrated improvements in biochemical markers and selected symptom measures, the broader real-world impact of elafibranor on multidimensional aspects of disease burden, including work productivity, activity impairment, emotional and social functioning, and the relationship between symptom trajectories and laboratory parameters, remains incompletely characterized.</p> <p>This study will address that evidence gap by generating longitudinal, real-world data among participants with PBC newly initiating elafibranor. Through prospective collection of participant-reported outcomes and medical record-derived laboratory data, this study will evaluate fatigue patterns over time, assess changes in pruritus and broader HRQoL domains, examine work productivity and activity impairment, and explore associations between symptom trajectories and biochemical markers in routine clinical practice.</p> |
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| <b>Study Timelines</b> | <p>Study Periods:</p> <ul style="list-style-type: none"> <li>• 10-month enrollment window (first participant in [FPI] to last participant in [LPI]), which may be shortened or increased by an additional 6 months, if agreed upon by the Sponsor and PicnicHealth.</li> <li>• Prospective Patient-Reported Outcomes (PRO): Participants may complete electronic PRO (ePRO) assessments at baseline (prior to or on the date of elafibranor initiation; a limited post-initiation completion allowance is described in Section 5.5) and at M3, M6, and M12 following treatment initiation. Each participant may be followed prospectively for 12 months for ePRO data collection; the M12 ePRO assessment may remain open for completion through the end of the overall study period.</li> <li>• Medical Record Collection: Medical record data will include both retrospective and prospective components. <ul style="list-style-type: none"> <li>- <b>Retrospective period:</b> Medical record retrieval at enrollment will provide visibility into clinical encounters prior to elafibranor initiation, subject to provider data retention policies. Retrospective data collection will include at least 5-7 years of all available clinical encounters prior to enrollment.</li> <li>- <b>Prospective period:</b> Medical records will be retrieved periodically following enrollment to capture laboratory values, treatment persistence, and concomitant medications documented as part of routine clinical care (secondary data). <ul style="list-style-type: none"> <li>(a) Medical record retrieval may continue through the end of the study data collection period (currently anticipated through March 2028, with the option to extend for up to three additional years upon agreement between PicnicHealth and the Sponsor).</li> </ul> </li> </ul> </li> </ul> |
| <b>Study Design:</b>   | <p>This study is conducted by PicnicHealth, the research vendor, on behalf of the Sponsor. PicnicHealth is responsible for participant recruitment, electronic informed consent, medical record retrieval and abstraction, ePRO administration, data management, and statistical analysis.</p> <p>This is a decentralized non-interventional, descriptive, real-world study of participants with PBC in the US who are newly initiating elafibranor with prospective primary data collection and retrospective data from medical records.</p> <p>This study is a direct-to-participant non-interventional study, and as such it has only a virtual site and no physical location.</p> <p>Participants will be informed about the study through multiple channels, which may include but are not limited to, the Ipsen Patient</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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|  | <p>Support Program (PSP), outreach to treating clinicians by medical science liaisons (MSLs), and participant advocacy groups. Additional recruitment sources may be added if agreed upon by PicnicHealth and Ipsen.</p> <p>Interested individuals will contact PicnicHealth directly and undergo a two-stage eligibility assessment. Under the Initial Screening Criteria, potentially eligible individuals will provide signed informed consent, complete an onboarding survey including self-reported demographic information, PBC diagnosis, and elafibranor status. Those who meet initial screening criteria will provide a medical record release authorization and complete the PBC-40 Fatigue Domain questionnaire. Participants who complete the PBC-40 Fatigue Domain will be considered to have met all Initial Screening Criteria and will proceed to the Full Enrollment Criteria stage. Participants across the PBC-40 Fatigue Domain spectrum will be eligible. The primary target for enrollment is participants with moderate-to-severe fatigue (PBC-40 Fatigue Domain score <math>\geq 29</math>), in alignment with the primary objective. The study population will comprise approximately 80% from the moderate-to-severe stratum, with up to approximately 10% from each of the mild (score of 12–28) and no/minimal (score <math>&lt;12</math>) fatigue strata included to support contextual interpretation. Actual proportions may vary based on screening yield and enrollment patterns; ratios for each strata might be adjusted following evaluation of enrollment patterns.</p> <p>Baseline ePRO assessments will be released following confirmation of Initial Screening Criteria and are to be completed prior to or on the date of participant self-report elafibranor initiation. For a maximum of 15 participants, completion up to 7 days following initiation is permitted; thereafter, all participants must complete baseline ePRO assessments prior to or on the date of elafibranor initiation.</p> <p>Full Enrollment Criteria will be confirmed through medical record review, including medical record-confirmed PBC diagnosis and documented elafibranor treatment or plan. Formal enrollment will be confirmed upon successful medical record review. Individuals who do not meet all Full Enrollment Criteria will be considered screen failures. These individuals will be part of the screened population and will be accounted for in the participant disposition summary as aggregate screening counts; their individual-level data will not be included in the participant-level study analyses. Discrepancies between medical record and patient confirmation of eligibility will be fully investigated to ensure no patients are erroneously coded as screen failures.</p> <p>Following confirmed enrollment, participants will be issued ePRO assessments at M3, M6, and M12 (at the corresponding appropriate timepoints) following elafibranor initiation. ePRO instruments may include but are not limited to: PROMIS Fatigue–SF 7a, PBC-40, WPAI-SHP, and WI-NRS.</p> |
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|                          | <p>In addition to collecting PRO data directly from participants, longitudinal clinical information will be extracted from medical records. Participants who discontinue elafibranor treatment will complete the ePRO assessment at the timepoint at which discontinuation is reported and will then be withdrawn from further prospective ePRO assessments. ePRO data collected up to and including this assessment will be retained and included in analyses; no further ePRO assessments will be administered thereafter. The date of discontinuation will be captured so the timing of this assessment relative to discontinuation can be determined.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Study Population:</b> | <p>This study will be conducted in the US and plans to enroll up to 50 participants with PBC who are newly initiating elafibranor. Participants across the full PBC-40 Fatigue Domain spectrum (any score) will be eligible. The primary target for enrollment is participants with moderate-to-severe fatigue (score <math>\geq 29</math>), in alignment with the primary objective; mild (score of 12–28) and no/minimal (score <math>&lt; 12</math>) cohorts will be included to support contextual interpretation. Actual proportions may vary based on screening yield and enrollment patterns; operational adjustments to these targets will not constitute a protocol deviation. Eligibility is confirmed through a two-stage process: self-report of key criteria at Initial Screening, followed by medical record review to confirm PBC diagnosis and elafibranor treatment at Full Enrollment. This sample size is considered sufficient to provide descriptive estimates of patterns in PROs (PROMIS Fatigue-SF 7a, PBC-40, WPAI-SHP, and WI-NRS) in participants with PBC receiving elafibranor. The final number of Enrolled participants may be lower or higher based on enrollment feasibility and Sponsor agreement.</p> <p><u>Initial Screening Criteria (self-report)</u></p> <ol style="list-style-type: none"> <li>(1) Self-reported diagnosis of PBC.</li> <li>(2) Age <math>\geq 18</math> years at the time of screening.</li> <li>(3) Self-reported treatment plan to initiate elafibranor, with no prior dose received before screening.</li> <li>(4) Completion of the PBC-40 Fatigue Domain at the time of screening.</li> <li>(5) Provided signed informed consent and medical record release authorization prior to data collection.</li> </ol> <p><u>Full Enrollment Criteria (medical record review)</u></p> <p>Participants are eligible to be included in the study only if all the following criteria apply:</p> <ol style="list-style-type: none"> <li>(1) Medical-record confirmed diagnosis of PBC.</li> <li>(2) Has a documented prescription or treatment plan to initiate elafibranor and has not received a prior dose of elafibranor before enrollment.</li> </ol> |

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|                           | <p><b><u>Exclusion Criteria</u></b></p> <p>Participants will not be included in the study if they meet any of the following criteria:</p> <ol style="list-style-type: none"> <li>(1) Unable to read and/or self-complete ePRO instruments or do not have a designee available to complete ePROs on their behalf.</li> <li>(2) Do not have access to a device on which ePRO instruments can be completed.</li> <li>(3) Self-reported participation in an interventional trial in PBC at the time of screening.</li> <li>(4) Failure to complete all required baseline ePRO assessments (PBC-40 and PROMIS Fatigue SF-7a). <ol style="list-style-type: none"> <li>(a) Baseline ePRO assessments are to be completed prior to or on the date of participant self-reported elafibranor initiation. For a maximum of 15 participants, completion up to 7 days following elafibranor initiation is permitted and will not constitute a protocol deviation; once 15 participants have used this post-initiation window, all subsequent participants must complete prior to or on the date of initiation.</li> </ol> </li> </ol> <p>Participants who self-report discontinuation of elafibranor at any ePRO time point will complete the ePRO assessment at that timepoint and will then be withdrawn from further prospective ePRO assessments; no further ePRO assessments will be administered thereafter. Treatment status will be confirmed through participant self-report; medical record documentation, if available, may be reviewed to provide context on treatment patterns but is not required to confirm withdrawal.</p> |
| <b>Study Treatment:</b>   | <p>This is a non-interventional study designed to collect data on the use of elafibranor in a real-world setting.</p> <p>The decision to prescribe elafibranor will be made prior to and independently from the decision to enroll a participant in this non-interventional study.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Study Evaluations:</b> | <p><b><u>Primary Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>• Scores at baseline (pre-initiation of elafibranor) and at M3, M6, and M12 and change from baseline (CfB) at M3, M6, and M12 for the PBC-40 Fatigue Domain.</li> <li>• Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for PROMIS Fatigue-SF 7a.</li> </ul> <p><b><u>Secondary Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>• Demographic and clinical characteristics of participants newly initiating elafibranor</li> <li>• Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WPAI-SHP domains (absenteeism, presenteeism, overall work impairment, and activity impairment).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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|                             | <ul style="list-style-type: none"> <li>Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for PBC-40 domains other than Fatigue (emotional, social, cognitive, general symptoms, and itch)</li> <li>Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WI-NRS.</li> </ul> <p><b><u>Exploratory Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>Values at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for liver function parameters (e.g., ALP, AST, ALT, bilirubin).</li> <li>Association between fatigue scores and liver function parameters (ALP, AST, ALT, and bilirubin) at baseline and at M3, M6, and M12.</li> <li>Association between PBC-40 Fatigue Domain score and PBC-40 domain scores other than Fatigue (cognitive, social, emotional, general symptoms, and itch) at baseline and at M3, M6, and M12.</li> <li>Association between PBC-40 Fatigue Domain score and WPAI-SHP domain scores (absenteeism, presenteeism, overall work impairment, and activity impairment) at baseline and at M3, M6, and M12.</li> <li>Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WPAI-SHP domains (absenteeism, presenteeism, overall work impairment, and activity impairment) stratified by age and clinical severity.</li> </ul> |
| <b>Statistical Methods:</b> | <p><b><u>Analysis sets:</u></b></p> <p>The Full Analysis Set (FAS) is anticipated to include all Enrolled participants who meet Full Enrollment Criteria, i.e. have a confirmed reference date (elaftibranor initiation), and have completed baseline PBC-40 and PROMIS Fatigue SF-7a. All FAS participants are expected to contribute to study analyses; missing follow-up data will be summarized as missing in the corresponding endpoints.</p> <p><b><u>Statistical analysis:</u></b></p> <p>This study is planned as a descriptive analysis and no <i>a priori</i> hypotheses testing is anticipated. Continuous variables will be summarized using descriptive statistics, including mean and 95% confidence interval (CI), standard deviation (SD), median and 95% CI, first and third quartiles, minimum, and maximum, as appropriate. Categorical variables may be summarized by frequency counts and percentages.</p> <p>The secondary and exploratory endpoints will be descriptively summarized. Actual values and change from baseline will be summarized for continuous endpoints. Shift tables will also be provided for categorical endpoints, if applicable.</p> <p>Missing patient reported outcomes (PRO) scores will be handled by the scoring algorithm. If conducted, sensitivity analyses with</p>             |

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|  | <p>imputation methods will be described in the SAP. Count and percentage of missing items will be reported.</p> <p>One interim analysis is planned (anticipated early 2027); it will be descriptive, focused on enrollment progress, feasibility, and preliminary trends, with scope and timing prespecified in the SAP.</p> <p>Further details on the analyses will be provided in the SAP.</p> |
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**2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

| <b>Abbreviation</b> | <b>Definition</b>                                                 |
|---------------------|-------------------------------------------------------------------|
| <b>ADR</b>          | Adverse Drug Reaction                                             |
| <b>AE</b>           | Adverse Event                                                     |
| <b>ALP</b>          | Alkaline Phosphatase                                              |
| <b>ALT</b>          | Alanine Aminotransferase                                          |
| <b>AMA</b>          | Anti-mitochondrial Antibody                                       |
| <b>AST</b>          | Aspartate Aminotransferase                                        |
| <b>CA</b>           | Competent Authorities                                             |
| <b>CfB</b>          | Change from baseline                                              |
| <b>CI</b>           | Confidence Interval                                               |
| <b>CRF</b>          | Case Report Form                                                  |
| <b>DMP</b>          | Data Management Plan                                              |
| <b>eCRF</b>         | Electronic Case Report Form                                       |
| <b>EDC</b>          | Electronic Data Capture                                           |
| <b>EP</b>           | Enrolled Population                                               |
| <b>ePRO</b>         | Electronic Patient-Reported Outcome                               |
| <b>FAS</b>          | Full Analysis Set                                                 |
| <b>FDA</b>          | U.S. Food and Drug Administration                                 |
| <b>FPI</b>          | First Participant In                                              |
| <b>HIPAA</b>        | Health Insurance Portability and Accountability Act               |
| <b>HRQoL</b>        | Health-Related Quality of Life                                    |
| <b>IRB</b>          | Institutional Review Board                                        |
| <b>LOINC</b>        | Logical Observation Identifiers Names and Codes                   |
| <b>LPI</b>          | Last Participant In                                               |
| <b>MELD</b>         | Model for End-Stage Liver Disease                                 |
| <b>MSL</b>          | Medical Science Liaison                                           |
| <b>PBC</b>          | Primary Biliary Cholangitis                                       |
| <b>PBC-40</b>       | Primary Biliary Cholangitis 40-Item Quality of Life Questionnaire |
| <b>PI</b>           | Prescribing Information                                           |

---

|                  |                                                                    |
|------------------|--------------------------------------------------------------------|
| <b>PPAR</b>      | Peroxisome Proliferator-Activated Receptor                         |
| <b>PRO</b>       | Patient-Reported Outcome                                           |
| <b>PROMIS</b>    | Patient-Reported Outcomes Measurement Information System           |
| <b>PSP</b>       | Patient Support Program                                            |
| <b>QMS</b>       | Quality Management System                                          |
| <b>SAE</b>       | Serious Adverse Event                                              |
| <b>SAP</b>       | Statistical Analysis Plan                                          |
| <b>SD</b>        | Standard Deviation                                                 |
| <b>SDV</b>       | Source Data Verification                                           |
| <b>SmPC</b>      | Summary of Product Characteristics                                 |
| <b>SMS</b>       | Short Message Service                                              |
| <b>SNOMED-CT</b> | Systematized Nomenclature of Medicine – Clinical Terms             |
| <b>SOP</b>       | Standard Operating Procedure                                       |
| <b>SP</b>        | Service Provider                                                   |
| <b>SS</b>        | Special Situation                                                  |
| <b>SSA</b>       | Social Security Administration                                     |
| <b>TFL</b>       | Tables, Figures and Listings                                       |
| <b>UDCA</b>      | Ursodeoxycholic Acid                                               |
| <b>US</b>        | United States                                                      |
| <b>WI-NRS</b>    | Worst Itch Numerical Rating Scale                                  |
| <b>WPAL-SHP</b>  | Work Productivity and Activity Impairment- Specific Health Problem |

### 3 INTRODUCTION

#### 3.1 Disease Review

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune cholestatic liver disease characterized by immune-mediated destruction of small intrahepatic bile ducts, leading to cholestasis, inflammation, fibrosis, and potentially cirrhosis if untreated [1]. PBC predominantly affects women and is most commonly diagnosed in middle adulthood [2].

In addition to progressive liver injury, PBC is associated with a substantial symptom burden. Fatigue and pruritus are among the most common and debilitating manifestations [2]. Fatigue affects up to 80% of participants, with approximately 20% experiencing severe, persistent fatigue that significantly impairs daily functioning and quality of life [2,3]. Pruritus is reported in 50–81% of participants, with approximately 30% experiencing clinically significant symptoms [4,5]. These symptoms frequently occur independently of biochemical disease severity and may present even in early-stage disease.

Fatigue and pruritus negatively impact health-related quality of life (HRQoL), including emotional well-being, cognitive functioning, sleep, social participation, and work productivity. Fatigue, in particular, remains under-recognized and undertreated, reflecting both its complex pathophysiology and limited effective therapeutic options.

In addition to symptom burden, PBC is characterized by biochemical abnormalities, including elevations in alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, which reflect cholestasis and hepatocellular injury. These laboratory parameters are clinically relevant indicators of disease activity and prognosis. While symptom burden and correlation to biochemical severity is not well understood, both biochemical abnormalities and symptoms contribute to overall disease impact and patient well-being.

#### Standard of Care (United States (US))

Ursodeoxycholic acid (UDCA) is the recommended first-line therapy for PBC. Although effective in slowing disease progression in many patients, up to 40% exhibit an inadequate biochemical response or intolerance [2].

For patients with inadequate response or intolerance to UDCA, second-line options include peroxisome proliferator-activated receptor (PPAR) agonists such as elafibranor and seladelpar, both approved by the US Food and Drug Administration (FDA) in 2024 [6,7].

Management of fatigue and pruritus remains largely supportive. While pruritus may be managed with bile acid sequestrants or other pharmacologic agents, there are no established therapies specifically approved for exclusively treating PBC-related fatigue. As a result, symptom burden remains a key unmet need in this population.

#### Research-Specific Medical Care Requirements

This is a non-interventional study. Treatment decisions, including initiation and continuation of elafibranor, will be made solely by treating physicians according to routine clinical practice. Study-related procedures are limited to:

- Collection of electronic participant-reported outcomes (ePROs) at baseline and M3, M6, and M12
- Retrieval and abstraction of medical records, including laboratory reports.

No protocol-mandated diagnostic or therapeutic interventions will be required.

### 3.2 Compound Review

Elafibranor received FDA approval in 2024 for the treatment of adults with PBC who have had an inadequate response or intolerance to UDCA.

Elafibranor is an oral dual PPAR- $\alpha/\delta$  agonist. Activation of PPAR- $\alpha$  and PPAR- $\delta$  regulates pathways involved in bile acid metabolism, lipid metabolism, inflammation, and fibrosis, thereby reducing cholestasis and improving biochemical markers associated with PBC [6].

The efficacy and safety of elafibranor in PBC were demonstrated in the pivotal Phase 3 ELATIVE trial [6]. In this randomized, placebo-controlled study, elafibranor significantly improved biochemical response compared with placebo.

In addition to biochemical improvements, elafibranor demonstrated clinically meaningful improvements in participant-reported outcomes. Improvements in pruritus were observed as measured by the PBC-40 itch domain and the 5-D Itch scale after 52 weeks of treatment. Post hoc analyses further demonstrated greater improvements in fatigue compared with placebo, as measured by PROMIS Fatigue-Short Form 7a and the PBC-40 fatigue domain. Among participants with moderate-to-severe fatigue at baseline, more than twice as many achieved clinically meaningful improvements compared with placebo [8].

While clinical trials have demonstrated improvements in biochemical markers and selected symptom measures, the broader impact of treatment on multidimensional aspects of disease burden, including cognition, emotional well-being, social functioning, and work productivity, has not been fully characterized in real-world settings.

### 3.3 Study Rationale

Although randomized clinical trials have demonstrated that elafibranor improves biochemical markers and selected participant-reported outcomes, the extent to which these improvements are associated with changes in fatigue, pruritus, cognition, emotional and social functioning, and work productivity in routine clinical practice remains incompletely characterized. Furthermore, the relationship between changes in laboratory parameters and symptom trajectories warrants evaluation in real-world settings.

Clinical trial populations are selected under strict eligibility criteria and structured follow-up schedules, which may limit generalizability. Moreover, it is expected that fatigue in PBC is multifaceted and may affect emotional well-being, social functioning, and work productivity that warrant evaluation in real-world settings.

This prospective, observational cohort study will generate longitudinal real-world data among participants with PBC newly initiating elafibranor in the US. Participant-reported outcome instruments, including but not limited to, PROMIS Fatigue-SF 7a, PBC-40, WPAI-SHP, and WI-NRS, will be administered at baseline and Months 3, 6, and 12 to:

- Characterize fatigue patterns following treatment initiation
- Assess changes in pruritus and HRQoL domains
- Evaluate work productivity and activity impairment
- Explore associations between symptom trajectories and laboratory parameters (ALP, ALT, AST, bilirubin)

The prospective design, with baseline assessments conducted prior to elafibranor initiation, enables within-participant evaluation of change over time in fatigue measures, which constitute the primary endpoints. The selected instruments are disease-relevant, and sensitive to change, with supporting psychometric evidence across relevant disease areas, ensuring that the collected data will directly address the study objectives.

Feasibility is supported by centralized medical record retrieval, ePROs administration, anticipated high response and retention rates, and a defined enrollment window and follow-up period.

The results of this study will provide real-world evidence regarding the impact of elafibranor on fatigue, pruritus, and HRQoL. These findings may inform clinical practice, support participant-centered treatment decisions, and contribute to health outcomes evaluations in PBC.

#### 4 OBJECTIVES AND ENDPOINTS

| Objectives                                                                                                                                                                                                                                                                                     | Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary</b>                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>To evaluate participant-reported fatigue values and patterns at baseline (pre-initiation of elafibranor) and through Month 3, Month 6, and Month 12 (M3, M6, and M12) after initiation of elafibranor for treatment of PBC (reference date).</li> </ul> | <ul style="list-style-type: none"> <li>Scores at baseline (pre-initiation of elafibranor) and at M3, M6, and M12 and CfB at M3, M6, and M12 for the PBC-40 Fatigue Domain.</li> <li>Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for PROMIS Fatigue SF-7a.</li> </ul>                                                                                                                                                                                                  |
| <b>Secondary</b>                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>To describe the demographic and baseline clinical characteristics of participants at the reference date.</li> </ul>                                                                                                                                     | <ul style="list-style-type: none"> <li>Demographic and clinical characteristics of participants newly initiating elafibranor, which may include: <ul style="list-style-type: none"> <li>Age</li> <li>Sex</li> <li>Race/ethnicity</li> <li>Geographic location</li> <li>Time since PBC diagnosis</li> <li>Disease severity (e.g., diagnosis of cirrhosis, PBC Stage)</li> <li>Laboratory values (e.g., ALT, AST, ALP, bilirubin)</li> <li>PBC-related medication history</li> </ul> </li> </ul> |
| <ul style="list-style-type: none"> <li>To evaluate participant-reported work productivity and activity impairment values and patterns at baseline and through M3, M6, and M12 after the reference date.</li> </ul>                                                                             | <ul style="list-style-type: none"> <li>Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WPAI-SHP domains (absenteeism, presenteeism, overall work impairment, and activity impairment).</li> </ul>                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>To evaluate PBC-40 domains other than Fatigue values and patterns at baseline and through M3, M6, and M12 after the reference date.</li> </ul>                                                                                                          | <ul style="list-style-type: none"> <li>Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for PBC-40 domains other than Fatigue (emotional, social, cognitive, general symptoms, and itch).</li> </ul>                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>To evaluate itch severity using the WI-NRS values and patterns at baseline and through M3, M6, and M12 after the reference date.</li> </ul>                                                                                                             | <ul style="list-style-type: none"> <li>Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WI-NRS.</li> </ul>                                                                                                                                                                                                                                                                                                                                                             |
| <b>Exploratory</b>                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>To describe liver function parameters (ALP, ALT, AST, and bilirubin) at</li> </ul>                                                                                                                                                                      | <ul style="list-style-type: none"> <li>Values at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for</li> </ul>                                                                                                                                                                                                                                                                                                                                                                     |

|                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| baseline and through M3, M6, and M12 after the reference date.                                                                                                                                                                             | liver function parameters (ALP, AST, ALT, bilirubin).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>To explore the association between liver function parameters (ALP, ALT, AST and bilirubin) and reported fatigue levels at baseline and through M3, M6, and M12 after the reference date.</li> </ul> | <ul style="list-style-type: none"> <li>Association between fatigue scores and liver function parameters (ALP, AST, ALT, and bilirubin) at baseline and at M3, M6, and M12.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>To explore the association between fatigue scores and other PBC-40 domain scores at baseline and through M3, M6, and M12 after the reference date.</li> </ul>                                       | <ul style="list-style-type: none"> <li>Association between PBC-40 Fatigue Domain scores and PBC-40 domain scores other than Fatigue (cognitive, social, emotional, general symptoms, and itch) at baseline and at M3, M6, and M12.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <ul style="list-style-type: none"> <li>To explore the association between fatigue scores and WPAI-SHP domain scores at baseline and through M3, M6, and M12 after the reference date.</li> </ul>                                           | <ul style="list-style-type: none"> <li>Association between PBC-40 Fatigue Domain scores and WPAI-SHP domain scores (absenteeism, presenteeism, overall work impairment, and activity impairment) at baseline and at M3, M6, and M12.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <ul style="list-style-type: none"> <li>To characterize WPAI-SHP domain scores in participants at baseline and through M3, M6, and M12 after the reference date, stratified by age and clinical severity.</li> </ul>                        | <ul style="list-style-type: none"> <li>Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WPAI-SHP domains (absenteeism, presenteeism, overall work impairment, and activity impairment) stratified by age and clinical severity.</li> <li>Age stratification, may include: <ul style="list-style-type: none"> <li>≤35 years</li> <li>36–49 years</li> <li>50–64 years</li> <li>≥65 years</li> </ul> </li> <li>Clinical severity, may include: <ul style="list-style-type: none"> <li>Normal: ALP ≤130 U/L and TB ≤20 µmol/L, no cirrhosis</li> <li>Mild-risk: ALP &gt;130 and ≤200 U/L and TB ≤ 20 µmol/L;</li> <li>Moderate-risk: ALP &gt; 200 U/L and TB ≤ 20µmol/L;</li> <li>High-risk: TB &gt;20 µmol/L or compensated cirrhosis (defined as kPa &gt;15).</li> </ul> </li> </ul> |

## 5 STUDY DESIGN

As this is a non-interventional study, the decision to prescribe elafibranor will be made by the treating physician prior to and independently from the participant's decision to participate in the study. Participation in the study will not influence treatment decisions, clinical management, or prescribing practices. All treatment decisions, including initiation and continuation of elafibranor, will be made by the treating physician in accordance with routine clinical practice and prior to, and independent of, the decision to participate in this study. Treating physicians are not study investigators, and no study-specific procedures will be required to justify or document prescribing decisions beyond routine clinical documentation.

### 5.1 Overview

#### Description of Design:

This is a decentralized non-interventional, descriptive, real-world study of adult participants with primary biliary cholangitis (PBC) who are newly initiating elafibranor in routine clinical practice in the US.

The study does not involve investigational sites. All data will be collected through medical record retrieval and ePROs assessments administered directly to participants.

Enrollment will occur in two stages. In the Initial Screening Criteria stage, potentially eligible individuals will be asked to provide signed informed consent. Following consent, participants will be asked to complete an onboarding survey including demographic information, self-reported PBC diagnosis, and elafibranor status. Individuals who meet initial screening criteria will then provide a medical record release authorization and complete the PBC-40 Fatigue Domain questionnaire to confirm fatigue level. Participants who complete the PBC-40 Fatigue Domain at screening, regardless of score, will be considered to have met this component of the Initial Screening Criteria and will proceed to the Full Enrollment Criteria stage. Enrollment across PBC-40 Fatigue Domain severity strata will be guided by the target distribution described in Section 5.2 (Enrollment Targets). Baseline ePRO assessments will be released following confirmation of Initial Screening Criteria. Participants will be asked to complete the baseline assessments prior to or on the date of elafibranor initiation. Operational flexibility regarding the baseline window is described in Section 5.5. Additionally, during the Full Enrollment Criteria stage, medical records will be retrieved to confirm all remaining enrollment criteria, including medical record-confirmed PBC diagnosis and documented elafibranor prescription. Discrepancies will be investigated to ensure no participants are erroneously not confirmed for full enrollment due to missing or delayed entry of information in medical records. Full enrollment will be confirmed upon completion of the medical record review process. Individuals deemed to not meet eligibility criteria at this stage will be considered screen failures and will not be included in study analyses.

Historical clinical data will be collected retrospectively at baseline through medical record retrieval to characterize prior disease history and baseline status. Participants will then be followed prospectively for 12 months following elafibranor initiation, with ePRO assessments at M3, M6, and M12. The M12 ePRO completion window will remain open through the end of the overall study period, and medical record data collection will continue through the same period to support follow-up data capture.

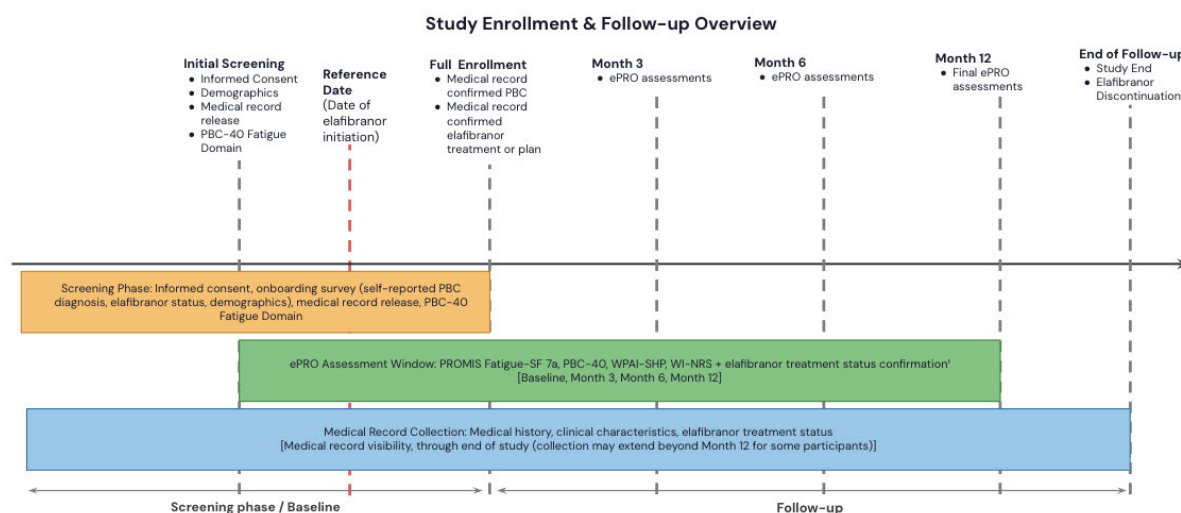
Elafibranor treatment, as initiated in routine clinical practice, constitutes the exposure of interest in this observational study. No treatment assignment or modification will be performed as part of the study.

The reference date for each participant will be defined as the date of elafibranor initiation. Data collected prior to the reference date will be designated as baseline data. Data collected after the reference date will be designated as follow-up data.

Participants will complete ePRO assessments at baseline (prior to or at treatment initiation) and at M3, M6, and M12 following treatment initiation.

This study is conducted by PicnicHealth on behalf of the Sponsor. PicnicHealth is responsible for recruitment, administration of electronic informed consent and medical record release authorization, retrieval and abstraction of medical records, administration and collection of ePRO assessments, data management, and statistical analysis. PicnicHealth conducts all analyses on the participant-level dataset and transmits only aggregated analytical outputs to the Sponsor; no participant-level data are transferred.

**Figure 1 Study Enrollment and Follow-Up**



<sup>1</sup> Treatment status confirmation administered at each ePRO timepoint; withdrawal triggered if elafibranor is discontinued

<sup>2</sup> As defined in the Data Model

Note: Withdrawal from the study may occur at any time during participation due to participant decision, elafibranor discontinuation, or other reasons.

### Description of modalities of participant recruitment:

Participants will be informed about the study through multiple recruitment channels, including but not limited to:

- The Ipsen Patient Support Program (PSP)
- Outreach to treating clinicians by Medical Science Liaisons (MSLs)
- Patient advocacy organizations

Additional recruitment sources may be added if agreed upon by PicnicHealth and Ipsen (the Sponsor). Potential participants will be informed about the study through enrollment channels mentioned above. Individuals who express interest will be directed to the PicnicHealth platform, where they may review study information and initiate the enrollment process.

Eligibility will be confirmed based on participant self-report and medical record documentation, including confirmation of PBC diagnosis and newly initiating elafibranor.

Enrollment will occur during a defined recruitment window of approximately 10 months, which may be shortened or expanded by up to an additional 6 months upon agreement by the Sponsor

and PicnicHealth. As this is a decentralized study without investigational sites, consecutive enrollment by investigators does not apply. Recruitment will be open to all eligible individuals who meet inclusion and exclusion criteria during the enrollment period.

Treating clinicians are not study investigators and will not be responsible for participant recruitment or study-specific data entry.

## 5.2 Population Characteristics

This study will enroll up to approximately 50 adult participants with a documented diagnosis of PBC who are newly initiating elafibranor in routine clinical practice. The final number of Enrolled participants may be lower or higher based on enrollment feasibility and Sponsor agreement.

Participants must meet the eligibility criteria outlined below in Section 6, including:

- Provided signed informed consent and medical record release authorization prior to data collection.
- Confirmed diagnosis of PBC
- Age  $\geq 18$  years
- Has a documented prescription or treatment plan to initiate elafibranor and has not received a prior dose of elafibranor before enrollment.
- Completion of the PBC-40 Fatigue Domain at screening
- Completion of required baseline ePRO assessments (PBC-40 and PROMIS Fatigue SF-7a)

## Enrollment Targets

The primary target for enrollment is participants with moderate-to-severe fatigue (PBC-40 Fatigue Domain score  $\geq 29$ ), in alignment with the primary objective of describing fatigue patterns in this population. The focus on moderate-to-severe fatigue as the primary target stratum is supported by post-hoc ELATIVE trial findings, in which participants with moderate-to-severe fatigue at baseline achieved clinically meaningful improvements with elafibranor at over twice the rate of placebo. This study aims to characterize fatigue patterns in this population in a real-world setting.

The study population will comprise approximately 80% from the moderate-to-severe stratum, with up to approximately 10% from each of the mild (12–28) and no/minimal ( $<12$ ) fatigue strata included to support contextual interpretation of findings.

Severity bands will follow validated PBC-40 Fatigue Domain thresholds (mild 12–28, moderate 29–39, severe  $\geq 40$ ). Actual proportions Enrolled may vary based on screening yield and enrollment patterns; there is no minimum enrollment requirement for any individual stratum. Enrollment will be monitored descriptively to assess representation across baseline fatigue severity categories. Operational adjustments to these targets will not constitute a protocol deviation.

## 5.3 Study Data Collection

Participants will be treated in accordance with usual medical practice during their participation in this study. No additional assessments or tests will be required by this protocol.

This study is non-interventional. Clinical and laboratory assessments will be collected only if performed as part of routine clinical care. If certain assessments are not performed in routine practice, no additional procedures will be required for study purposes.

Relevant data collected as part of routine medical care will be captured on an electronic Case Report Form (eCRF) and other structured data outputs derived from participants' medical records, as applicable. PicnicHealth will conduct all analyses on the participant-level dataset. Only aggregated analytical outputs (summary tables, figures, and statistical results as specified in the Statistical Analysis Plan (SAP)) will be transmitted to the Sponsor. No participant-level data will be transferred.

PicnicHealth will generate study data for a predefined set of data elements that are identified in the Study Data Model. This data will originate from PROs, which will be administered and collected electronically via the PicnicHealth platform, and participant's medical records. The operationalizing of the medical-record-derived data elements that will support the study objectives will be finalized during the Study Data Model development. Data elements may include but are not limited to the variables described below.

**Table 1 Summary of data domains and representative data elements**

| Collection Methods                             | Data domain                  | Example data elements                                                                                                  | Collection Frequency        | Data Origin                                     |
|------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------|
| EHR-generated (via medical record abstraction) | PBC Diagnosis                | PBC (diagnosis, start date)                                                                                            | Once at baseline            | Medical records                                 |
|                                                | PBC comorbidities & symptoms | Liver fibrosis, cirrhosis, decompensated cirrhosis, osteoporosis, PBC symptoms                                         | Once at baseline            | Medical records                                 |
|                                                | Other comorbidities          | Myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, COPD (Charlson-type comorbidities) | Once at baseline            | Medical records                                 |
|                                                | PBC-related treatments       | Elafibranor, UDCA, OCA, seladelpar, linerixibat (start/stop dates, stop reason)                                        | Multiple (every occurrence) | Medical records (+ self-report for elafibranor) |
|                                                | Laboratory results           | AMA, ANA, ALP, AST, ALT, bilirubin (collection date, value)                                                            | Multiple (every occurrence) | Medical records                                 |
|                                                | PBC-related assessments      | Child-Pugh score, MELD, PBC stage (Nakanuma), ELF score, liver stiffness/FibroScan (kPa)                               | Once at baseline            | Medical records                                 |

|                                                                     |                     |                                                                                          |                                        |                |
|---------------------------------------------------------------------|---------------------|------------------------------------------------------------------------------------------|----------------------------------------|----------------|
| Primary / Non-abstracted<br>(participant-reported & study-recorded) | Demographics        | Birth year, sex, race, ethnicity, state of residence                                     | Once at baseline                       | Self-report    |
|                                                                     | ePROs               | PBC-40 Fatigue Domain (screening), PROMIS Fatigue SF-7a, PBC-40 (full), WPAI-SHP, WI-NRS | Baseline + Follow-up (M3, M6, and M12) | Self-report    |
|                                                                     | Study participation | Enrollment date, withdrawal date/reason, death date, study visits                        | Once / every occurrence                | Study-recorded |

#### 5.4 Study Data Collection Flow

As this is a non-interventional study, treatment with elafibranor, the nature and timing of study assessments, and data collection will be conducted as per routine clinical practice.

The planned ePRO assessments and collection of medical record data obtained as part of routine clinical care are presented in [Table 2](#). No additional assessments or tests will be required for the purpose of this study.

Table 2 Schedule of Data Collection

| Collected data                                              | Collection timepoints |                 |                            |         |         |          |                                            |
|-------------------------------------------------------------|-----------------------|-----------------|----------------------------|---------|---------|----------|--------------------------------------------|
|                                                             | Initial Screening     | Full Enrollment | Baseline (Pre-Initiation)* | Month 3 | Month 6 | Month 12 | Ongoing after enrollment through study end |
| Informed Consent and medical record retrieval authorization | X                     |                 |                            |         |         |          |                                            |
| Self-attestation of eligibility criteria                    | X                     |                 |                            |         |         |          |                                            |
| Self-attestation of demographics                            | X                     |                 |                            |         |         |          |                                            |
| PBC-40 confirmation of fatigue severity                     | X                     |                 |                            |         |         |          |                                            |
| Medical record confirmation of clinical eligibility         |                       | X               |                            |         |         |          |                                            |
| PROMIS Fatigue-SF 7a                                        |                       |                 | X                          | X       | X       | X        |                                            |
| WPAI-SHP                                                    |                       |                 | X                          | X       | X       | X        |                                            |
| WI-NRS                                                      |                       |                 | X                          | X       | X       | X        |                                            |
| Full PBC-40                                                 |                       |                 | X                          | X       | X       | X        |                                            |
| PBC Diagnosis                                               |                       | X               | X                          |         |         |          |                                            |
| PBC comorbidities & symptoms**                              |                       |                 | X                          | X       | X       | X        |                                            |
| PBC-related treatment**                                     |                       |                 | X                          | X       | X       | X        |                                            |
| Laboratory Results**                                        |                       |                 | X                          | X       | X       | X        |                                            |
| PBC-related assessments**                                   |                       |                 | X                          |         |         |          |                                            |
| PBC-related procedures**                                    |                       |                 | X                          |         |         |          |                                            |
| Reported Adverse Events***                                  |                       |                 |                            |         |         |          | X                                          |
| Participant Status (Withdrawal/Completion)                  |                       |                 |                            |         |         |          | X                                          |

\*Baseline ePRO assessments are intended to be completed prior to or on the date of participant self-report elafibranor initiation and before the first dose. Baseline medical record data include information documented prior to or on the reference date.

\*\*PBC comorbidities, symptoms, treatments, laboratory results, assessments, and procedures will be collected only if available as part of routine clinical practice. The frequency and timing of these assessments may vary across participants. These data will not be actively collected at specific study timepoints; rather, available clinical data will be analytically anchored to the relevant assessment windows (M3, M6, M12) per rules defined in the SAP.

\*\*\*Adverse events will be collected following enrollment and throughout the duration of the study when reported by participants to PicnicHealth.

Please note that the clinical characteristics will be gathered from all available medical records, reflecting the participant's medical care during routine clinical practice. As such, the participant's clinical journey will be characterized as of M3, M6, and M12 after the reference date, but any given assessment may occur with varying frequency. The SAP will detail the approach to assign records within a dedicated visit.

## **5.5 Study Data Collection Timing and Methods**

Two data collection phases will occur:

### **Enrollment and Baseline Assessments**

#### Stage 1: Initial Screening Criteria

Potentially eligible individuals will first provide signed electronic informed consent. Following consent, participants will complete an onboarding survey, including basic demographic information, self-reported PBC diagnosis, and elafibranor status. Participants who meet these criteria will then provide medical record release authorization, after which they will complete the PBC-40 Fatigue Domain questionnaire. Participants who complete the PBC-40 Fatigue Domain, regardless of score, will be considered to have met all Initial Screening Criteria and will proceed to the Full Enrollment Criteria stage. The PBC-40 Fatigue Domain score will be used to support stratified enrollment management; see Section 5.2 (Enrollment Targets) for the target distribution and operational approach.

The baseline ePRO assessment window will open following confirmation of Initial Screening Criteria and will close upon participant self-report of elafibranor initiation. Self-report of initiation will be captured via a brief confirmation survey administered periodically during the screening period. Participants will be asked to complete baseline ePRO assessments prior to or on the date of elafibranor initiation, as confirmed by participant self-report. To prevent loss of baseline data due to missed pre-initiation completion, a maximum of 15 participants may complete baseline ePRO assessments up to 7 days following elafibranor initiation. Once 15 participants have completed baseline ePRO assessments within this post-initiation window, all subsequent participants must complete baseline ePRO assessments prior to or on the date of elafibranor initiation. This limited allowance is supported by the expectation that elafibranor's pharmacologic effect on fatigue is not fully established within the first 7 days following initiation, such that ePRO scores within this window are reflective of pre-treatment status.

#### Stage 2: Full Enrollment Criteria

Following medical record release authorization, medical records will be retrieved to confirm all remaining full enrollment criteria, including medical-record-confirmed diagnosis of PBC and documented elafibranor treatment or plan. Full enrollment will be confirmed upon successful medical record review. Individuals who do not meet all eligibility criteria upon medical record review will be considered screen failures and will not be included in the analysis. Discrepancies will be investigated to ensure no participants are erroneously not confirmed for full enrollment due to missing or delayed entry of information in medical records.

Upon confirmed enrollment, participants will have:

- Provided authorization for retrieval of medical records
- Completed the PBC-40 Fatigue Domain
- Met all Initial Screening Criteria as confirmed through self-report
- Been offered all baseline ePRO assessments
- Met all Full Enrollment Criteria as confirmed through medical record review

Baseline data will include demographic information, medical history, baseline laboratory parameters, and prior medications.

### **Follow-up**

Participants will be followed prospectively for 12 months following elafibranor initiation. Medical record collection and the M12 ePRO completion window may continue through the expected end of data collection in March 2028. The analytically relevant follow-up period for specific objectives will be defined in the SAP. If agreed upon between PicnicHealth and the Sponsor, the overall follow-up window may be extended by up to three additional years.

The two data sources differ in their contribution to follow-up:

#### Medical Record Data

At the time of enrollment, medical record retrieval will provide visibility into participants' retrospective clinical encounters across their sites of care. The date range of available clinical encounters will depend on individual provider data retention policies; however, multiple years of historical data prior to enrollment are expected to be available for most participants.

PicnicHealth will retrieve medical records periodically throughout the study until the participant withdraws consent, discontinues elafibranor, is removed from the study, or the end of the data collection period (currently anticipated through March 2028), whichever occurs first. Medical record retrieval is intended to capture clinical data corresponding to each participant's full follow-up period, including any late M12 ePRO completions; see Section 5.7 for additional detail.

While the specific data elements to be abstracted will be finalized in the Study Data Model, medical record-derived data are expected to include relevant clinical information from the period prior to elafibranor initiation and through the end of data collection. For analytic purposes, emphasis is anticipated to focus on clinical encounters occurring within approximately one year prior to elafibranor initiation and during prospective follow-up; final analytic windows will be specified in the SAP.

#### Participant-Reported Outcomes

The ePRO data will be collected prospectively through electronic assessments administered via the PicnicHealth platform. Baseline ePRO assessments are intended to be completed prior to or on the date of elafibranor initiation. Follow-up ePRO assessments will be administered at M3, M6, and M12 following elafibranor initiation. Participants may receive reminder notifications to complete scheduled assessments.

The ePRO data collection will be limited to the prospective study period and does not include retrospective reporting prior to enrollment. Participants who discontinue elafibranor treatment will complete the ePRO assessment at the timepoint at which discontinuation is reported and will then be withdrawn from further prospective ePRO assessments. ePRO data collected up to and including this assessment will be retained and included in analyses; no further ePRO assessments will be administered thereafter. The date of discontinuation will be captured so the timing of this assessment relative to discontinuation can be determined. This assessment is completed within the standard assessment window for that timepoint (M3, M6, or M12).

The ePRO data collected during the study will contribute to analyses anchored to the scheduled post-initiation timepoints (M3, M6, M12). The M12 ePRO completion window will remain open through the end of the overall study period. For analytical purposes, ePRO data are anchored to their scheduled timepoint regardless of calendar date of completion. The specific analytic time windows and handling of incomplete or missing PRO data will be prespecified in the SAP.

### Confirmation of Elafibranor Initiation

Elafibranor initiation will be ascertained through participant self-report.

Participants will be contacted periodically through the secure study platform, email, SMS, or telephone to ascertain whether and when elafibranor treatment has begun. Self-report of initiation will trigger operational study transitions, including closure of the baseline ePRO window (described above in Section 5.5) and the participant's transition to the follow-up phase.

Baseline ePRO assessments must be completed prior to or on the date of participant self-report of elafibranor initiation (and before first dose whenever feasible). For a maximum of 15 participants, completion up to 7 days following initiation is permitted; thereafter, all participants must complete baseline ePRO assessments prior to or on the date of initiation. Once initiation is confirmed, participants will transition to the follow-up phase.

Medical record documentation of an elafibranor prescription or treatment plan is required to confirm Full Enrollment Criteria (Section 6). Medical record documentation may also be used to support determination of the initiation date for analytical purposes. Rules for analytical reference date are described in Section 5.6 and will be specified in the SAP.

### Elafibranor Discontinuation

At each scheduled ePRO timepoint (M3, M6, and M12), participants will also be asked to confirm their current elafibranor treatment status via a single-item question. Participants who report discontinuation of elafibranor will complete the ePRO assessment at that timepoint and will then be withdrawn from further prospective ePRO assessments; data collected up to and including this assessment will be retained for analysis. Participants reporting discontinuation will also be asked the date of elafibranor discontinuation, where known.

Elafibranor end date will be captured from both the participant self-report at each ePRO timepoint and medical record documentation, when available. In cases where both sources are available, predefined adjudication rules will be specified in the SAP.

## **5.6 Data Sources**

Data for this study will be obtained from two primary sources: (1) medical records (secondary data) and (2) ePRO instruments (primary data).

### **Medical Records (Secondary Data Source)**

Historical and ongoing medical records will be retrieved from healthcare providers following participant authorization. Records may include documentation from hepatology, gastroenterology, primary care, laboratory services, and other relevant clinical settings involved in the participant's care.

Retrieved records will be curated and structured within the PicnicHealth platform using standardized data abstraction procedures. Extracted variables may include, but are not limited to:

- PBC Diagnosis: date of PBC diagnosis
- PBC comorbidities and symptoms: liver fibrosis, cirrhosis of liver, decompensated cirrhosis of liver, osteoporosis
- PBC-related treatments: elafibranor, UDCA, obeticholic acid (OCA), seladelpar, fenofibrate, cetirizine, cholestyramine resin, colesevelam, colestipol, cyproheptadine, desloratadine, diphenhydramine, fexofenadine, hydroxyzine, loratadine, naloxone, naltrexone, phenobarbital, rifampin, sertraline, linerixibat
  - Drug start and end dates and stop reason (when present) may be captured.

- Laboratory results: anti-mitochondrial antibody (AMA), PBC-specific antinuclear antibody (ANA), ALP, AST, ALT, GGT, total bilirubin, conjugated bilirubin, international normalized ratio (INR), serum albumin, serum sodium, serum potassium
- PBC-related assessments: PBC Stage, MELD score, Child-Pugh (CP) score
- PBC-related procedures: Liver transplant

The reference date for analysis will be defined as the date of elafibranor initiation, with medical record documentation generally serving as the primary source. Specific rules for source data prioritization and discrepancy handling will be defined in the SAP.

Medical record data will reflect routine clinical documentation. No additional diagnostic or laboratory assessments will be performed for study purposes. As medical record data will reflect routine clinical documentation, completeness, timing, and frequency of recorded assessments may vary across participants and providers. No additional assessments will be performed for study purposes.

In addition, death will be ascertained through multiple sources, including but not limited to: medical record review, caregiver attestation, social security administration (SSA) limited access death master file, and commercially available mortality vendors such as Veritas.

### **Electronic participant-Reported Outcomes (Primary Data Source)**

Primary study data will be collected directly from participants through electronic participant-reported outcome instruments administered via a secure electronic platform.

The following instruments will be administered at baseline (prior to or at elafibranor initiation) and at M3, M6, and M12 post-initiation (see Section 15):

- **PROMIS Fatigue–Short Form 7a:** A 7-item instrument designed to assess the frequency and severity of fatigue and its impact on daily functioning over the past seven days. Scores are standardized (T-scores), with higher scores indicating greater fatigue severity.
- **PBC-40:** A validated, disease-specific health-related quality-of-life questionnaire developed for participants with primary biliary cholangitis. It includes multiple domains, including fatigue, itch, cognitive, emotional, social functioning, and general symptoms. Domain scores reflect symptom burden and disease impact in the last four weeks, with higher scores indicating greater impairment.
- **WPAI-SHP:** An instrument used to assess the impact of health problems on work productivity and regular activities. It provides measures on the following domains: absenteeism, presenteeism, overall work productivity loss, and activity impairment over the preceding seven days.
- **WI-NRS:** A single-item participant-reported numeric rating scale that assesses the severity of worst itch experienced in the past seven days. Participants rate their worst itch on a scale from 0 (no itch) to 10 (worst itch imaginable). The WI-NRS 24-hour recall version has been used as an itch endpoint in PBC clinical trials, including the ELATIVE trial. Higher scores indicate greater itch severity.

Participants will complete assessments remotely using a personal device. Completion of the baseline PBC-40 Fatigue Domain assessment is required to determine study eligibility. Participants who discontinue ePRO completion may be considered lost to prospective follow-up. Participants may decline to complete any individual assessment or withdraw from the study

at any time. Participants may receive reminders to complete scheduled study assessments. Reminders will be operational prompts to complete study activities; they do not include questions about health status, symptoms, or adverse events, and ePRO instruments are not administered during reminder contact. Reminder modalities may include secure study-platform notifications, email, and SMS and, where permitted under applicable pharmacovigilance guidance and by agreement between the Sponsor and PicnicHealth, may also include direct participant contact (e.g., telephone). The specific modalities that will be used are operational; changes to the modalities used, including the addition or removal of direct telephone contact, do not constitute a protocol amendment. At study start, reminders may be limited to non-telephone modalities pending confirmation of the applicable safety-reporting approach (see Section 10).

The PRO data will be time-stamped and linked to curated medical record data using a unique participant identifier within the study database.

Baseline ePRO assessment window will open at Initial Screening Criteria confirmation and will close upon initiation of elafibranor. For up to 15 participants, this window may remain open up to 7 days following elafibranor initiation; thereafter, completion must be prior to or on the date of initiation (see Section 5.5). Follow-up ePRO assessment window will open at the designated timepoint (M3, M6, and M12 post-elafibranor initiation) and will remain open until the subsequent scheduled timepoint. The M12 survey window will remain open until study completion, which is anticipated in March 2028. The ePRO windows may be adjusted if agreed upon by the Sponsor and PicnicHealth.

Medical record data and ePRO data will be integrated into a unified, de-identified analytic dataset at the participant level. All analyses will be conducted using this integrated dataset.

### **Treatment Initiation Date Determination**

The date of elafibranor initiation (reference date) will be determined based on available source data, with medical record documentation generally serving as the primary source. Participant-reported initiation dates will be used operationally during the study to confirm initiation and trigger study transitions (e.g., closure of the baseline ePRO window). For analytical purposes, specific rules for determining the final reference date, including handling of discrepancies between participant self-report and medical record documentation, will be defined in the SAP. Operational decisions made based on participant self-report (e.g., baseline window closure) will not be re-adjudicated retroactively.

## **5.7 Study Duration/Observation Period**

The study will be considered to have started when the first participant provides signed informed consent.

The planned enrollment period is approximately 10 months. If necessary to achieve the target sample size, the enrollment period may be extended following agreement between the Sponsor and PicnicHealth. Any such extension will be documented through internal study documentation and, where required, communicated to applicable regulatory bodies in accordance with local requirements.

The prospective follow-up period for each participant is anticipated to be 12 months from elafibranor initiation. ePRO assessments will be triggered at M3, M6, and M12 post-initiation. The M3 and M6 ePROs must be completed within a pre-specified assessment window around each scheduled timepoint. The M12 ePRO will remain open for completion through the end of the overall study period (anticipated March 2028). As a result, the interval between elafibranor initiation and M12 ePRO completion may exceed 12 months for some participants. Medical

record collection may extend beyond the 12-month follow-up window through the end of the overall study period to capture clinical data, laboratory results, and any events relevant to the study endpoints during this extended window.

The overall study duration may extend beyond the initial projected timeline depending on the pace of enrollment, duration of follow-up, and any agreed-upon extension of the data collection period. The study will be considered complete at the end of the data collection period (currently anticipated to be March 2028 and potentially extendable by up to 3 additional years upon agreement between PicnicHealth and the Sponsor), after all study-related data have been collected, cleaned, and finalized for analysis.

## **5.8 Participant Information**

Prior to enrollment, participants will receive detailed information regarding the nature and purpose of the study. As all clinical care will occur in accordance with routine medical practice and no study-mandated procedures are required, participation does not impose additional clinical risks beyond those associated with standard treatment.

Written informed consent will be obtained electronically prior to enrollment and prior to any study-related data collection.

Participants will be provided with a copy of their signed informed consent form. The consent form may be revised during the study if new information becomes available that may affect participants' willingness to continue participation.

Treating physicians are not study investigators and are not responsible for obtaining informed consent.

## 6 STUDY POPULATION

This study will enroll adult participants in the United States with a documented diagnosis of PBC who are newly initiating elafibranor in routine clinical practice.

As this is a descriptive, non-interventional study, no formal sample size calculation has been performed. The study is expected to enroll approximately 50 participants. The final sample size may be lower or higher than the target based on operational considerations such as recruitment yield, data completeness, and ongoing alignment between the Sponsor and PicnicHealth. Such adjustments are operational in nature and will not constitute a protocol deviation or require a formal protocol amendment. All participants must meet the inclusion and exclusion criteria defined below.

Initial screening and eligibility confirmation will be conducted following electronic informed consent and prior to full enrollment in the analysis population.

Eligibility is confirmed through a 2-stage process: self-report of key criteria at Initial Screening, followed by medical record review to confirm PBC diagnosis and elafibranor treatment at Full Enrollment. Only participants who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study.

### 6.1 Inclusion Criteria

#### Initial Screening Criteria (self-report)

- (1) Self-reported diagnosis of PBC.
- (2) Age  $\geq 18$  years at the time of screening.
- (3) Self-reported treatment plan to initiate elafibranor, with no prior dose received before screening.
- (4) Completion of the PBC-40 Fatigue Domain at the time of screening.
- (5) Stratified enrollment targets will be applied, see Section 5.2 (Enrollment Targets) for the target distribution and operational management.
- (6) Provided signed informed consent and medical record release authorization prior to data collection.

#### Full Enrollment Criteria (confirmed via medical record review)

- (1) Medical-record confirmed diagnosis of PBC.
- (2) Documented prescription or treatment plan to initiate elafibranor and has not received a prior dose of elafibranor before enrollment.

### 1.1 Exclusion Criteria

Participants will not be included in the study if they meet any of the following criteria:

- (1) Unable to read and/or self-complete electronic ePRO instruments or do not have a designee available to complete ePROs on their behalf.
- (2) Do not have access to a device on which ePRO instruments can be completed.
- (3) Self-reported participation in an interventional trial in PBC at the time of screening.
- (4) Failure to complete required baseline ePRO assessments (PBC-40 and PROMIS Fatigue SF-7a).
  - (a) The baseline window closes on the date of elafibranor initiation. For up to 15 participants, completion of baseline ePRO assessments up to 7 days following elafibranor initiation is permitted; once 15 participants have used this post-

initiation window, all subsequent participants must complete prior to or on the date of initiation.

## 6.2 Participant Withdrawal Criteria

As this is a non-interventional study, participants will be managed according to routine clinical practice by their treating physicians. No protocol-defined clinical withdrawal criteria apply to treatment decisions.

Participation in this study is voluntary. Participants may withdraw their consent at any time without penalty or impact on their clinical care.

Because this is a decentralized study and treating physicians are not study investigators, withdrawal from the study will occur under the following circumstances:

- Participant request to withdraw consent
- Discontinuation of elafibranor treatment, including transition to an alternative PBC-specific therapy (e.g., seladelpar), as this study is specifically designed to evaluate the real-world impact of elafibranor on fatigue, work productivity, and related outcomes; continued participation following discontinuation of elafibranor would not meaningfully contribute to the primary study objectives.
  - Treatment discontinuation will be confirmed via a single-item ePRO question administered prior to each survey timepoint (M3, M6, and M12), asking participants to confirm whether they are still receiving elafibranor treatment. Participants who report discontinuation will complete the ePRO assessment at that timepoint and will then be withdrawn from further prospective ePRO assessments; the reported discontinuation date will be captured where known. This assessment is completed within the standard assessment window for that timepoint (M3, M6, or M12).
- Sponsor decision to discontinue the study
- Administrative or regulatory reasons

Upon withdrawal of consent or removal from the study, no additional prospective data (including ePROs or medical record retrieval) will be collected as of the date the withdrawal is reported. For participants withdrawn due to elafibranor discontinuation, the ePRO assessment completed at the timepoint discontinuation is reported is retained and included in analyses (see Section 5.5). Medical record data will be collected and retained through the date of discontinuation; records covering this period may be retrieved after discontinuation is reported. No medical record data pertaining to the period after discontinuation will be collected.

Data collected prior to withdrawal may be retained and used for analysis in accordance with the informed consent form and applicable regulations, unless the participant explicitly requests removal of previously collected data, where permissible by law.

## **7 STUDY ENDPOINT AND EVALUATIONS**

### **7.1 Study Endpoints and Evaluations**

This study is descriptive in nature. Detailed statistical methods, handling of missing data, analysis populations, and exploratory analyses will be specified in the SAP.

#### **7.1.1 Coprimary Endpoint**

- Scores at baseline (pre-initiation of elafibranor) and at M3, M6, and M12 and CfB at M3, M6, and M12 for the PBC-40 Fatigue Domain.
- Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for PROMIS Fatigue SF-7a.

Fatigue will be assessed using ePRO instruments, PBC-40 and PROMIS Fatigue SF-7a, completed by participants at predefined study timepoints. Baseline fatigue scores will reflect assessments completed prior to or on the date of elafibranor initiation (reference date).

#### **7.1.2 Secondary Endpoints**

##### **Demographic and Clinical Characteristics**

- Demographic and clinical characteristics of participants newly initiating elafibranor
  - Age
  - Sex
  - Race/ethnicity
  - Geographic location
  - Time since PBC diagnosis
  - Disease severity (diagnosis of cirrhosis, PBC Stage)
  - Laboratory values (ALT, AST, ALP, bilirubin)
  - PBC-related medication history

##### **WPAI-SHP**

- Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WPAI-SHP domains (absenteeism, presenteeism, overall work impairment, and activity impairment)

##### **PBC-40 Domains**

- Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for PBC-40 domains other than Fatigue (cognitive, social, emotional, general symptoms, and itch).

##### **Worst Itch-Numeric Rating Scale (WI-NRS)**

- Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WI-NRS.

#### **7.1.3 Exploratory Endpoints**

##### **Liver Function Parameters**

- Values at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for liver function parameters (ALP, AST, ALT, and bilirubin).
- Association between fatigue scores (PBC-40 Fatigue Domain and PROMIS Fatigue SF-7a) and liver function parameters (ALP, AST, ALT, and bilirubin) at baseline and at M3, M6, and M12.

##### **PBC-40**

- Association between PBC-40 Fatigue Domain score and PBC-40 domains other than Fatigue scores (cognitive, social, emotional, general symptoms, and itch) at baseline and at M3, M6, and M12.

**WPAI-SHP**

- Association between PBC-40 Fatigue Domain score and WPAI-SHP domain work productivity scores (absenteeism, presenteeism, overall work impairment, and activity impairment) at baseline and at M3, M6, and M12.
- Scores at baseline and at M3, M6, and M12 and CfB at M3, M6, and M12 for WPAI-SHP domains (absenteeism, presenteeism, overall work impairment, and activity impairment) stratified by age and clinical severity.
  - Age stratification, may include:
    - $\leq 35$  years
    - 36–49 years
    - 50–64 years
    - $\geq 65$  years
  - Clinical severity, may include:
    - Normal: ALP  $\leq 130$  U/L and TB  $\leq 20$   $\mu\text{mol/L}$ , no cirrhosis
    - Mild-risk: ALP  $> 130$  and  $\leq 200$  U/L and TB  $\leq 20$   $\mu\text{mol/L}$ ;
    - Moderate-risk: ALP  $> 200$  U/L and TB  $\leq 20$   $\mu\text{mol/L}$ ;
    - High-risk: TB  $> 20$   $\mu\text{mol/L}$  or compensated cirrhosis (defined as kPa  $> 15$ ).

## **8 TREATMENTS OF INTEREST**

This is an observational study designed to collect data on the use of elafibranor in real-world clinical practice.

The decision to prescribe elafibranor will be made prior to and independently of the decision to enroll the participant in this non-interventional study.

## 9 STATISTICAL CONSIDERATIONS

The information provided in this section may be subject to change and will be finalized in the SAP. The SAP will be developed as a separate document and approved prior to the database freeze date for the interim analysis (IA) and will contain detailed descriptions of the planned statistical analyses, including Tables, Figures, and Listings (TFL) shells and derivation rules.

This study is descriptive in nature. Analyses are intended to characterize longitudinal patterns in participant-reported outcomes and clinical variables following elafibranor initiation in routine clinical practice. No formal hypothesis testing is planned unless otherwise prespecified in the SAP.

### 9.1 Participant Classification and Definitions

**Screened participant:** An individual who has provided informed consent and has initiated initial screening.

**Enrolled participant (included participant):** A screened participant who meets all Full Enrollment Criteria and none of the exclusion criteria, as confirmed by screening information and medical record documentation.

**Reference date:** The date of elafibranor initiation. Medical record documentation will generally serve as primary source, with specific rules for source data prioritization and handling discrepancies between participant reports defined in the SAP. Operational decisions made based on participant self-report (e.g., closure of baseline ePRO window) will not be re-adjudicated retroactively.

**Baseline period:** All data collected prior to or on the reference date. Baseline PROs are those completed prior to or on the reference date (and before first dose whenever feasible).

**Follow-up period:** All data collected after the reference date through 12 months post-initiation, with allowable assessment windows around each scheduled ePRO timepoint (M3, M6, M12) specified in the SAP. ePRO assessments may be anchored to their scheduled post-initiation timepoint (M3, M6, M12) for analysis, regardless of the calendar date of completion. The M12 ePRO, once triggered, may be completed through the end of the overall study period. Medical record collection may continue through the end of the overall study period to ensure complete capture of clinical data, laboratory values, and relevant events corresponding to each participant's full follow-up period, including late M12 ePRO completions.

**Withdrawn participant:** A participant who ceases participation in the study prior to completing the planned 12-month follow-up period (e.g., withdrawal of consent, loss to follow-up, administrative reasons).

**Treatment discontinuation:** Discontinuation of elafibranor (including transition to an alternative therapy) as self-reported by the participant via ePRO, with supporting context from medical record documentation when available. Given that the study objective is to evaluate the impact of elafibranor treatment on participant-reported outcomes, discontinuation of elafibranor will result in withdrawal from study participation. Data collected up to and including the assessment at the timepoint will be retained for analysis.

### 9.2 Definition of Analyses Populations

Analysis populations will be defined in detail in the SAP. The SAP will specify the exact inclusion criteria for each analysis population, including handling of missing data, allowable assessment windows, and definition of protocol deviations.

The following analysis populations are anticipated:

**Full Analysis Set (FAS) / Primary Analysis Population**

The FAS is anticipated to include all Enrolled participants who meet all Full Enrollment Criteria as confirmed through medical record review and who have:

- Confirmed initiation of elafibranor (reference date), and
- Completed baseline PBC-40 and PROMIS Fatigue SF-7a assessments.

All FAS participants will contribute to study analyses. Missing follow-up data will be summarized as missing in the corresponding endpoint outputs. Imputation methods, if applied, will be limited to sensitivity analyses and will be defined in the SAP.

#### **Additional Analysis Sets (if applicable)**

Additional analysis populations (e.g., domain-specific analysis sets, completer population, or modified analysis sets) may be defined in the SAP if warranted by data completeness patterns or analytic considerations. Any such definitions will be finalized prior to the interim analysis and will not alter the predefined study endpoints.

#### **9.2.1 Populations Analysed**

The primary study endpoint analyses may be conducted using the FAS, as defined in this protocol and further detailed in the SAP.

Supportive and sensitivity analyses may be conducted using additional analysis populations, if applicable. The SAP will specify the analysis population used for each endpoint and analysis.

#### **9.2.2 Participant Allocation and Reasons for Exclusion from the Analyses**

Participants will be allocated to analysis populations based on predefined criteria specified in the SAP.

Any exclusions from specific analysis sets will be based on objective criteria prespecified in the SAP.

### **9.3 Sample Size Determination**

This study is descriptive in nature and is not designed or powered to test formal statistical hypotheses.

The planned enrollment of up to approximately 50 participants is based on feasibility considerations and the rarity of primary biliary cholangitis, as well as the objective of characterizing longitudinal changes in participant-reported fatigue and related outcomes following elafibranor initiation in routine clinical practice. The final number of Enrolled participants may be lower or higher based on enrollment feasibility and Sponsor agreement.

A sample size of approximately 50 participants is expected to provide sufficient precision to describe distributions and changes over time in fatigue scores (PROMIS Fatigue-SF 7a and PBC-40 Fatigue Domain), as well as secondary participant-reported outcomes. Precision of descriptive estimates (e.g., confidence intervals around mean changes or proportions) will be reported where appropriate.

Enrollment will be guided by a target fatigue severity distribution at baseline (severity bands: mild 12–28, moderate 29–39, severe  $\geq 40$ ). The primary target for enrollment is participants with moderate-to-severe fatigue (PBC-40 Fatigue Domain score  $\geq 29$ ), comprising approximately 80% of total enrollment, in alignment with the primary objective. The mild (score of 12–28) and no/minimal (score  $< 12$ ) strata, each up to approximately 10% of total enrollment, are included to support contextual interpretation. All Enrolled participants meeting Full Analysis Set criteria will contribute to study analyses; stratum-specific descriptive summaries will be presented as defined in the SAP. Because approximately 80% of enrollment is targeted to the moderate-to-severe fatigue stratum, the study population is not representative of all elafibranor initiators; accordingly, the principal interpretation of fatigue-related findings

will focus on the moderate-to-severe baseline fatigue stratum, and overall summaries for the full Enrolled population will be presented descriptively and interpreted with caution. Final study composition may differ based on screening yield and enrollment patterns; operational adjustments to these targets will not constitute a protocol deviation.

The final number of evaluable participants will depend on enrollment rates, confirmation of eligibility, and follow-up completion. The sample size may be decreased or increased if agreed upon by the Sponsor and PicnicHealth. No formal interim sample size re-estimation is planned. Tracking of enrollment will be conducted to ensure appropriate distribution of baseline self-reported Fatigue Domain score categories. Adjustments to the target enrollment based on findings from the interim analysis may be considered by agreement between the Sponsor and PicnicHealth, as described in Section 9.5 (Interim Analysis).

#### 9.4 Statistical and Analytical Methods

A SAP describing the planned statistical analysis in detail with TFLs shells will be developed as a separate document. The SAP will serve as the governing document for analysis populations, endpoints, and statistical methods.

Statistical analyses are anticipated to be performed using R (R Core Team) or other validated statistical software, as appropriate.

As this is a non-interventional study, analyses are primarily descriptive in nature, and no formal hypothesis testing is expected. When appropriate, two-sided 95% CIs may be presented. Any p-values, if reported, will be considered exploratory and interpreted descriptively. All analyses are descriptive; confidence intervals, where presented, are intended to describe the precision of the sample estimates and should not be interpreted as supporting confirmatory inference to a broader target population.

Descriptive statistics may include the number of available and missing observations and the following, as appropriate:

- Mean, standard deviation (SD), minimum, median, maximum, first and third quartiles, and 95% CIs as appropriate for continuous variables;
- Counts and percentages for categorical variables, with corresponding 95% CIs.

Percentages will generally be based on the number of non-missing observations. For categorical endpoints, shift tables relative to baseline may also be presented, as applicable.

Visit windows and the rules for assigning ePRO and medical-record-derived assessments to baseline, M3, M6, and M12 will be prespecified in the SAP, including rules for instances where multiple observations occur within a single visit window.

Missing data will not be routinely imputed. Missing item responses within PRO instruments will be handled according to the relevant instrument scoring manuals. Missing scheduled assessments at M3, M6, or M12 will not be imputed in the primary descriptive analyses unless otherwise specified. For each endpoint and timepoint, the number of missing observations will be summarized. Sensitivity analyses assessing alternative assumptions for missing follow-up data, and any handling of incomplete dates, will be prespecified in the SAP.

Each ePRO instrument will be scored according to published scoring algorithms. For multi-domain instruments (e.g., PBC-40), domain-specific scores will be derived.

For exploratory objectives evaluating associations between liver function parameters and participant-reported outcomes, analyses may include descriptive and exploratory methods such as correlation analyses and regression modelling (e.g., linear or generalized linear models), as appropriate based on the distribution and structure of the data. The specific modelling

approaches, covariate adjustments, and handling of repeated measures will be prespecified in the SAP.

The main analysis of pruritus-related endpoints (e.g., WI-NRS and the PBC-40 itch domain) may be conducted on a subset of participants without confounding pruritus-targeting therapies during the follow-up period. PBC-related therapies specifically targeting pruritus (e.g., ileal bile acid transporter inhibitors approved for cholestatic pruritus, or pharmacologic therapies prescribed for pruritus) will be captured from medical records and used to define this subset. Participants receiving pruritus-targeting therapies during follow-up will be summarized separately. The specific operational definitions of pruritus-targeting therapies, the timing window, and the subset-definition rules will be defined in the SAP.

#### **9.4.1 Demographic and Other Baseline Characteristics**

Baseline demographic and clinical characteristics will be summarized descriptively for enrolled participants and for the FAS, where applicable.

Variables may include, but are not limited to:

- Age
- Sex
- Race/ethnicity
- Geographic region
- Time since PBC diagnosis
- Disease severity
- Liver function parameters
- PBC-related medication history
- Baseline ePRO scores

#### **9.4.2 Participant Disposition and Withdrawals**

Participant accountability will be summarized to provide a clear flow from consent through the analysis populations.

Screening and enrollment accountability may be reported as aggregate operational counts derived from screening and recruitment tracking; these individuals are not included in the participant-level analysis dataset. Counts may include the number of individuals who:

- consented;
- pre-screened (participant has both provided informed consent and successfully attested to meeting all inclusion/exclusion criteria);
- screened (participant has been partially qualified and passed at least one inclusion/exclusion criterion); and
- enrolled (participant has been fully qualified and enrolled in the program after passing record review).

For enrolled participants, disposition may be summarized descriptively on the FAS, including:

- Number and percentage of participants, completed, discontinued, withdrawn and reason for withdrawal
- Number and percentage of participant per ePRO assessment timepoint, including duration of participation in the study
- Number and percentages of participants included in each analysis set with reasons for exclusion from each analysis set

As this is a decentralized study conducted in the US, tabulation by centre is not applicable.

### **9.4.3 Study Analysis**

#### **9.4.3.1 Primary analysis**

Primary endpoints include longitudinal fatigue outcomes measured by:

- PBC-40 Fatigue Domain
- PROMIS Fatigue–SF 7a

For each coprimary endpoint, the primary descriptive analysis will summarize observed PBC-40 Fatigue Domain and PROMIS Fatigue SF-7a scores at baseline, M3, M6, and M12, and change from baseline at M3, M6, and M12, among participants in the Full Analysis Set with data available at the relevant timepoint. Baseline is defined according to the protocol-specified baseline window (Section 5.5). Follow-up assessments will be assigned to nominal visits according to the predefined visit windows in the SAP. Participants who discontinue elafibranor contribute data collected up to and including the assessment at the timepoint at which discontinuation is reported; no further ePRO data are collected thereafter.

#### **9.4.3.2 Secondary analysis**

Secondary endpoints include:

- WPAI-SHP
- PBC-40 Emotional Domain, Social Domain, Cognitive Domain, General Symptoms Domain, and Itch Domain
- WI-NRS

For each secondary endpoint, scores and change from baseline will be descriptively summarized at M3, M6, and M12 on the FAS with data available at the relevant timepoint. Baseline is defined according to the protocol-specified baseline window (Section 5.5), and follow-up assessments will be assigned to nominal visits according to the predefined visit windows in the SAP. Participants who discontinue elafibranor contribute data collected up to and including the assessment at the timepoint at which discontinuation is reported; no further ePRO data are collected thereafter. Summaries are observed-case in nature.

The SAP will specify endpoint-specific scoring and derivation rules, allowable assessment windows, and handling of missing data. Additional descriptive summaries (e.g., distributions and categorical severity groupings based on prespecified thresholds) may be presented as specified in the SAP.

#### **1.1.1.1 Exploratory analysis**

Exploratory endpoints include descriptive evaluation of liver function parameters (e.g., ALP, ALT, AST, bilirubin), and exploration of associations between fatigue and other participant-reported or clinical outcomes, as defined in the Study Endpoints (Section 4).

Exploratory analyses will be descriptive in nature and may include summary statistics and graphical presentation of trends over time.

For exploratory objectives evaluating associations between liver function parameters and participant-reported outcomes, analyses may be evaluated descriptively and cross-sectionally at each nominal timepoint (baseline, M3, M6, and M12) using observed scores. Associations between change from baseline in liver function parameters and change from baseline in participant-reported outcomes may also be explored. Methods may include correlation analyses and regression modelling (e.g., linear or generalized linear models), as appropriate based on the distribution and structure of the data. The specific parameters and scores evaluated, modelling

approaches, covariate adjustments, and handling of repeated measures and missing data will be prespecified in the SAP. Results of exploratory analyses will be interpreted descriptively and not as confirmatory evidence.

Stratified summaries of WPAI-SHP domain scores by age and clinical severity are exploratory and descriptive. If subgroup sample sizes are small, categories may be combined or suppressed, as prespecified in the SAP.

### **9.5 Interim Analysis**

One interim analysis is planned for this study. The IA is anticipated to be conducted in early 2027, based on a dataset created in February 2027, though the exact timing may be adjusted and will be confirmed in the SAP. Only analytical outputs will be delivered to the Sponsor.

The IA will be descriptive in nature and will focus on enrollment progress, baseline characteristics, study feasibility, and preliminary trends in primary study endpoints. No formal hypothesis testing will be performed unless otherwise specified in the SAP.

Based on the findings of the IA, the study team may consider a protocol modification to adjust the target enrollment or enrollment procedures to meet study objectives. Any such decision will be made in accordance with criteria prespecified in the SAP.

The scope, timing, statistical methods, and decision criteria for the interim analysis will be fully prespecified in the SAP.

## 10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS AND SPECIAL SITUATIONS

This study is derived primarily from secondary data. While the study includes a primary data collection component in the form of ePROs, these instruments are structured and closed-ended and do not include open-ended response options through which participants may report adverse events (AEs).

PicnicHealth will not actively solicit safety information, conduct systematic review of medical records to identify adverse events, perform medical review or adjudication, or conduct follow-up investigations related to safety events.

Adverse events and special situations (SSs) that come to PicnicResearch's attention may be reported to Ipsen Global Pharmacovigilance as follows:

- (1) **Unsolicited participant contact:** a participant independently contacts PicnicHealth to report an AE or SS. Reported as a spontaneous report.
- (2) **Information volunteered during operational participant contact** (e.g., assessment reminders): a participant spontaneously mentions an AE or SS during reminder contact initiated by PicnicHealth. Reported using the applicable pathway as agreed between the Sponsor and PicnicHealth.

In such cases, the event will be reported to Ipsen Global Pharmacovigilance in accordance with the timelines described below.

The safety plan may be adjusted as agreed upon by the Sponsor and PicnicHealth and will be formalized in the Safety Management Plan document.

### 10.1 Definition

#### 10.1.1 Adverse Event

| AE Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>An AE is any untoward medical occurrence in a participant, administered a medicinal product (elafibranor) and which does not necessarily have a causal relationship with this treatment.</p> <p>An AE may therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Events Meeting the AE Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p>Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).</p> <p>Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</p> <p>New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study.</p> <p>Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</p> <p>Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse</p> |

event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

For studies involving marketed products in established indications include:

The signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of effectiveness” or “failure of expected pharmacological action” also constitutes an AE or SAE.

#### Events NOT Meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

PicnicHealth will not independently assess causality, seriousness, or expectedness.

#### 10.1.2 *Serious Adverse Event*

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

PicnicHealth will not independently determine seriousness. All reported events will be forwarded to Ipsen, and Ipsen will determine seriousness and regulatory reporting obligations in accordance with its pharmacovigilance procedures.

#### **An SAE is defined as any serious adverse event that, at any dose:**

(a) Results in death

(b) Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

(c) Requires inpatient hospitalisation or prolongation of existing hospitalisation

In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out participant setting. Complications that occur during hospitalisation are AEs. If a complication prolongs

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether “hospitalisation” occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.                                                                                                                                                                                                                                                                                                                           |
| <p>(d) Results in persistent or significant disability/incapacity</p> <p>The term disability means a substantial disruption of a person’s ability to conduct normal life functions.</p> <p>This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.</p>                                                                                                                      |
| (e) Is a congenital anomaly/birth defect                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p>(f) Other situations:</p> <p>Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.</p> <p>Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.</p> |
| (g) Is a suspected transmission of any infectious agent via an authorised medicinal product                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

### 10.1.3 “Special Situations”

Special situation is any incidence of drug exposure during pregnancy (i.e. drug exposure to a foetus in utero (whether the foetus is exposed via the mother taking the product or transmission via semen following paternal exposure) or breastfeeding, overdose, off label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic effectiveness whilst using the medicinal product.

PicnicHealth will report to Ipsen any “special situation” whether or not these “special situations” are associated with an AE.

#### 10.1.3.1 Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, and Medication Error

**Note:** Consistent with the safety data collection method for this study (see Section 10.2.1), PicnicHealth does not review medical records or conduct active surveillance to identify these special situations. Overdose (including use exceeding the recommended dose), off-label use, misuse, abuse, occupational exposure, and medication error will be captured and reported to Ipsen only if reported by the participant. Events identified through any other source will not be reported.

Where a special situation described in this section is reported by a participant, it will be reported to Ipsen Global Pharmacovigilance whether or not it is associated with a clinical event, within 7 calendar days, using the applicable Ipsen reporting form for non-interventional studies, as agreed between the Sponsor and PicnicHealth and specified in the Safety Management Plan.

***Overdose***

Any dose higher than the maximum recommended dose in local label/SmPC, or in the protocol. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime in the protocol, or labelling text will be assessed as 'overdose'. Overdoses should be reported as AEs whether or not they were associated with a clinical event.

***Off-label Use***

Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Off-label use should be reported as AEs whether or not they were associated with a clinical event.

***Misuse***

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

Misuse should be reported as AEs whether or not they were associated with a clinical event.

***Abuse***

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Abuse should be reported as AEs whether or not they were associated with a clinical event.

***Occupational exposure***

Occupational exposure refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Occupational exposure should be reported.

***Medication error***

Medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

Medication error should be reported as AEs whether or not they were associated with a clinical event.

**10.2 Time Period and Frequency for Collecting and Reporting AE, SS and SAE Information**

For the definition of the AEs and SS, please refer to Section [10.1](#).

The collection and reporting of AEs will follow regulations related to non-interventional studies. For this secondary use of data study, the submission of individual case safety reports (ICSRs) is not required, and expedited reporting of SAEs/ADRs and SSs to Ipsen Global Pharmacovigilance is not required. AEs reported during the study period as defined in the study protocol will be collected, and safety-relevant results will be provided on an aggregate level in the study report.

Table 3 Safety Event Reporting

| Safety Event       | Reported to Ipsen Global Pharmacovigilance                                                       |
|--------------------|--------------------------------------------------------------------------------------------------|
| Non-serious AE     | Yes, if identified via unsolicited report or volunteered during operational participant contact. |
| SAE                | Yes, if identified via unsolicited report or volunteered during operational participant contact. |
| Special Situations | Yes, if identified via unsolicited report or volunteered during operational participant contact. |

**NOTE:** Events are identified incidentally and reported to Ipsen as described above. PicnicHealth will not conduct follow-up or investigations on any reported event.

### 10.2.1 Collection of Safety Information

The collection and reporting of AEs will follow regulations related to non-interventional studies.

PicnicHealth may collect and report AEs and SSs identified through the following mechanisms:

- (1) **Unsolicited participant contact:** where a participant directly contacts PicnicHealth to report an AE or SS.
- (2) **Information volunteered during operational participant contact** (e.g., assessment reminders): a participant spontaneously mentions an AE or SS during reminder contact initiated by PicnicHealth. Reported using the applicable pathway as agreed between the Sponsor and PicnicHealth.

PicnicHealth will:

- Capture all information provided at the time of the report
- Not actively solicit additional safety details
- Not conduct follow-up or medical investigation
- Not perform causality, seriousness, or expectedness determinations

All available information at the time of identification will be reported to Ipsen PV.

### 10.2.2 Timelines for Safety Information Reporting to Sponsor Pharmacovigilance

Timelines for reporting to the Sponsor are as follows:

- Within 1 business day of PicnicHealth's knowledge of any reported AE or SS.

All adverse events will be processed by the Sponsor according to their relevant Standard Operating Procedures.

### Mandatory Information for Reporting an AE:

The following information is the minimum that must be provided to Ipsen's Pharmacovigilance contact within 24 hours for an AE:

- Participant identifier
- Product name

- Adverse event description
- Recorder and contact details

The additional information included in the AE report form must be provided to Ipsen as soon as it is available.

### **10.3 Process for Reporting to Ipsen Pharmacovigilance**

PicnicHealth will report all applicable AEs and SSs using the applicable Ipsen reporting form for non-interventional studies, as agreed between the Sponsor and PicnicHealth, submitted by e-mail to Ipsen Global Pharmacovigilance within the timelines above:

**Email:** adverse.events@ipsen.com

The minimum information provided with each report will include:

- Participant identifier
- Product name (ela fibranor)
- Adverse event or SS description
- Recorder name and contact details

Once the safety form has been completed and submitted to Ipsen Global Pharmacovigilance, it will be saved as a PDF and uploaded to the relevant sponsor portal on the PicnicHealth Research Platform. Additional details on safety reporting will be found in the Safety Management Plan.

### **10.4 Ipsen Reporting Requirements to Regulatory Authorities**

Ipsen is responsible for analyzing all safety information received and reporting to regulatory agencies as determined by country-specific legislation or regulations. The expectedness of an AE will be determined by Ipsen using reference safety information specified in the product label (Summary of Product Characteristics (SmPC)/Prescribing Information (PI)) for elafibranor. If the product has marketing authorisations in several countries with different SmPCs or PIs, one will be selected by the Ipsen study team as the reference document for assessing expectedness, agreed with the Ipsen pharmacovigilance representative.

## **11 STUDY MANAGEMENT**

### **11.1 Monitoring Procedures**

This is a decentralized, non-interventional study conducted without investigational sites. Therefore, traditional on-site monitoring visits are not applicable.

PicnicHealth will oversee study conduct in accordance with this protocol, applicable regulatory requirements, and internal quality management procedures.

Sponsor oversight may include periodic review of study progress, enrollment metrics, data completeness, and safety reporting in accordance with the study agreement and Safety Management Plan. No participant-level data, identifiable or de-identified, will be provided to the Sponsor.

Study oversight activities may include remote review of analytical outputs, study reports, and quality control metrics.

### **11.2 Recording of Study Data**

All study data will be collected and maintained within PicnicHealth's secure electronic systems. Participants will complete electronic informed consent and ePRO assessments directly through the secure PicnicHealth platform using personal devices.

Medical record data will be retrieved following participant authorization and curated within PicnicHealth's proprietary electronic data capture (EDC) system.

Data entered into the system will be saved to a centralized database with an electronic audit trail to track data creation and modifications.

Access to study systems will be restricted to authorized personnel through secure authentication procedures, including unique usernames and passwords.

### **11.3 Data Verification**

This is a decentralized, non-interventional study conducted without investigational sites. Traditional on-site source data verification (SDV) is not applicable.

All medical record data used for this study will be obtained directly from healthcare providers following participant authorization and curated within PicnicHealth's secure data systems.

Data verification will occur centrally through structured data abstraction processes and quality control procedures, as described in the Data Management section. Verification activities may include:

- Review of source medical record documents during abstraction
- Cross-checking of abstracted variables against source documentation
- Verification of key study variables, may include:
  - Confirmation of PBC diagnosis
  - Confirmation of elafibranor initiation date (reference date)
  - Primary and secondary endpoint data elements

Because medical records are retrieved and stored centrally within PicnicHealth's secure systems, and because no participant-level data will be transferred to the Sponsor, Sponsor-authorized personnel will not perform direct review of source medical records or participant-level datasets. Sponsor oversight may consist of review of analytical outputs and the methodologies used to produce them, as documented in the SAP.

Participants provide authorization for retrieval and use of their medical records as part of the informed consent process. Access to identifiable information will be limited to authorized

PicnicHealth personnel and as required, the Institutional Review Board (IRB), study monitors, regulatory authorities, and individuals responsible for safety oversight (including adverse event monitoring), in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and applicable data protection regulations.

#### **11.4 Data Quality**

The accuracy of data abstracted from participant medical records is ensured through a range of measures leveraging both technology and human expertise. PicnicHealth's data abstraction platform is designed to flag irregularities and low confidence outputs using conservative thresholds that minimize false-negatives. Flagged irregularities and outputs are reviewed by clinically trained chart abstractors.

PicnicHealth's curators complete a structured training program and must successfully demonstrate proficiency before taking on full curation responsibilities. All research data may be reviewed by additional curators using a risk-based approach to identify data elements in need of additional review based on the study variable's criticality and complexity, and individual and aggregated data can also be subject to review by data engineers, biostatisticians, and clinicians. Difficult data elements or scenarios that are not described in standard procedures can be escalated to a senior team lead, per policy.

Participant-reported outcome data are captured directly through the secure study platform and stored in the study database. Data integrity measures such as timestamping, authentication, and validation of successful data transfer are applied; however, participant responses are not altered.

PicnicHealth's risk-based, fit-for-purpose Quality Management System (QMS) is guided by four principles: participants First, Technology Excellence, Data Integrity, and Sound Research. To support these principles, PicnicHealth deploys tactics including continuous process improvement, training, issue and risk management, and verification.

PicnicHealth logs data transformations and performs regular internal data quality audits. The data quality is continuously monitored and analyzed for quality throughout the retrieval and abstraction process. Additional details regarding data quality procedures will be described in the Data Management Plan.

#### **11.5 Data Management**

##### ***11.5.1 Medical Record Data***

###### **Collection and Storage**

Copies of participants' medical records are obtained from source healthcare systems and health information exchanges using PicnicHealth's record request platform. Record request forms, along with participants' authorization for release of records, are provided to healthcare provider offices and followed up as needed. Records are obtained as part of routine clinical care.

PicnicHealth receives copies of medical records in various formats, including but not limited to electronic data transfers, secure e-faxes, paper records, and compact disks. While medical records share essential components, records from different care sites vary in structure and detail.

Records returned by fax are received via secure e-fax. Mailed records are scanned, verified, and uploaded to PicnicHealth's secure servers. Electronic data transfer is conducted through secure, encrypted connections.

All medical records are stored securely in accordance with HIPAA and applicable data protection regulations.

### Data Curation and entry

PicnicHealth curates' data from medical records through a structured, multi-step process. Each source file may be segmented into individual clinical documents, including provider notes, diagnostic reports, laboratory results, and other relevant documentation. Clinical documents may be further divided into sections to enable targeted data abstraction.

Clinical concepts and important metadata fields are abstracted using a combination of proprietary artificial intelligence models and clinically trained chart abstractors. Abstracted concepts are mapped to standard medical ontologies, including but not limited to:

- Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT)
- Logical Observation Identifiers Names and Codes (LOINC)

If a standard ontological code is not available for an extracted concept, a custom code may be assigned.

PicnicHealth compiles data across sites of care to generate a single, de-identified longitudinal view of each participant's care.

Curated data are entered into PicnicHealth's proprietary internal EDC system in accordance with eCRF guidelines. Data entered into the EDC system are saved to a central database, and all changes are tracked to provide a complete audit trail.

### ***11.5.2 Electronic participant-Reported Outcome Data***

#### Collection and Storage

Electronic participant-reported outcome data are collected directly from participants through PicnicHealth's secure, web-based platform using a mobile-enabled device or computer.

Participants complete instruments at predefined study timepoints as described in the protocol. Survey data are entered directly by the participant into the platform and are time-stamped at submission.

All PRO data are transmitted via secure, encrypted connections and stored on PicnicHealth's secure servers in accordance with applicable data protection regulations.

#### Data Handling

The PRO data are entered directly by participants and do not require transcription.

The PRO data are linked to curated medical record data using a unique participant identifier within the study database.

Instrument scoring will follow published scoring algorithms. Detailed derivation rules and handling of item-level missing data will be specified in the SAP.

#### Data Cutoffs for Interim and Final Analyses

For any planned interim or final analyses, predefined data cutoffs will be applied to ensure completeness and data quality of the underlying dataset.

For medical record-derived data, the retrieval cutoff is expected to occur approximately 8–12 weeks prior to analytical dataset finalization to allow sufficient time for record receipt, abstraction, quality review, and database finalization.

For participant-reported outcomes (ePROs), the data cutoff is expected to occur approximately 2 weeks prior to analytical dataset finalization to allow for processing and quality checks.

Following analytical dataset finalization, statistical analyses will be conducted per the SAP, and analytical outputs will be delivered to the Sponsor.

Specific timelines for data cutoffs and the schedule for delivery of analytical outputs will be documented in the Data Management Plan and/or SAP. Minor adjustments to cutoff timing may occur as operationally necessary and will not constitute a protocol deviation.

#### **11.6 Record Archiving and Retention**

Details of the approach to record retention will be included in the study Data Management Plan.

## **12 ETHICAL CONSIDERATIONS, REGULATORY FRAMEWORK, AND ADMINISTRATION PROCEDURES**

### **12.1 Ethical and Regulatory Considerations**

This study is a non-interventional, observational research study conducted in the US. The study does not involve assignment of investigational treatments, protocol-mandated clinical interventions, or alteration of routine medical practice.

The study will be conducted in accordance with:

- The ethical principles set forth in the Declaration of Helsinki
- The International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP) Guidelines [9]
- Applicable United States federal and state regulations governing human subjects' research
- The Health Insurance Portability and Accountability Act (HIPAA) of 1996 and related privacy regulations

Because treatment decisions are made independently of study participation and no study-mandated clinical procedures are required, this study is considered non-interventional.

### **12.2 Institutional Review Board (IRB) Approval**

Prior to initiation of the study, the protocol, informed consent form, recruitment materials, and any participant-facing materials will be submitted to an IRB for review and approval, as required by applicable regulations.

No study activities will begin until written IRB approval has been obtained.

Ongoing IRB reporting will be conducted in accordance with IRB requirements, including submission of amendments, annual continuing review reports (if applicable), and reporting of unanticipated problems or reportable events.

### **12.3 Informed Consent**

Written informed consent will be obtained electronically from each participant or their legally authorized representative (LAR) prior to enrollment and prior to any study-related data collection.

The informed consent process will include:

- Explanation of the study purpose and procedures
- Description of data collection (medical records and ePROs)
- Authorization for retrieval of medical records
- Description of data privacy protections
- Voluntary nature of participation

Participants will receive a copy of the signed informed consent form.

### **12.4 Publication Policy**

Ipsen is committed to disclosing information about the studies it sponsors. Results will be communicated at scientific meetings, and all reasonable efforts must be made to seek publication in a peer-reviewed scientific journal.

Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate Ipsen Global Publications Manager and incorporated in the relevant publication plan before initiation.

As a minimum, summary results of this study should be posted on the relevant study registry. Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines [10]. In particular, those named as authors, whether employed by Ipsen or an Ipsen affiliate, or external investigators, ‘should have participated sufficiently in the work to take public responsibility for the content’.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Each author must agree to their inclusion in the list of authors. Use of professional medical writing support may be employed.

Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

All publications arising from this study will be reviewed by relevant functions at Ipsen, coordinated by the Global Publications team as per the applicable SOP. Requests and suggestions for changes will be discussed with all authors (and medical writers, if applicable). Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. Review comments must be answered before a final version for submission can be approved by the author team.

## **12.5 Study Report**

A study report will be prepared in compliance with any applicable regulatory requirements, national laws in force. It should be written in English.

## **12.6 Contractual and Financial Details**

The study will be conducted under a written agreement between Ipsen (the Sponsor) and PicnicHealth (the research provider), outlining the respective roles, responsibilities, deliverables, and financial terms associated with the conduct of the study.

The agreement will define responsibilities related to study execution, data collection, data analysis, safety reporting, publication, and regulatory compliance.

Financial arrangements between the Sponsor and PicnicHealth, including payment schedules and scope of work, will be specified in the applicable study agreement. No payments will be made to treating physicians, as they are not study investigators and are not responsible for participant recruitment or study-specific procedures.

Participants will not incur costs related to study participation beyond routine clinical care.

### **13        PROTOCOL AMENDMENTS**

Any substantive modification to the protocol will be documented in a formal protocol amendment.

All proposed amendments will be reviewed and approved by the Sponsor prior to implementation. Where required, amendments will be submitted to the IRB for review and approval before implementation, in accordance with applicable regulations.

Amendments will not be implemented until all required approvals have been obtained, except where necessary to eliminate immediate hazards to participants.

Administrative or minor changes that do not affect study design, participant safety, or data integrity may be documented without requiring formal amendment, as permitted by applicable regulations and IRB policies.

All amendments will be summarized in the Protocol Amendment History section.

**14 BIBLIOGRAPHIC REFERENCES**

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**15 LIST OF APPENDICES****15.1 Appendix 1: PBC-40 Questionnaire****SYMPTOMS DOMAIN**

1. I was able to eat what I liked
  - a. Coding (reverse): Never=5, Rarely=4, Sometimes=3, Most of the time=2, Always=1
2. I ate or drank only a small amount and still felt bloated
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
3. I felt unwell when I drank alcohol
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5, Does not apply=0
4. I had discomfort in my right side
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
5. I had dry eyes
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
6. My mouth was very dry
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
7. I had aches in the long bones of my arms and legs
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5

**ITCH DOMAIN**

8. Itching disturbed my sleep
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5, Does not apply=0
9. I scratched so much I made my skin raw
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5, Does not apply=0
10. I felt embarrassed because of the itching
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5, Does not apply=0

**FATIGUE DOMAIN**

11. I had to force myself to get out of bed
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
12. I had to have a sleep during the day
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
13. Fatigue interfered with my daily routine
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
14. I felt worn out
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
15. I felt so tired I had to force myself to do the things I needed to do
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
16. I felt so tired I had to go to bed early
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
17. Fatigue just suddenly hit me
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
18. PBC drained every ounce of energy out of me
  - a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5

19. Some days it took me a long time to do anything  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
20. If I was busy one day I needed at least another day to recover  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
21. I had to pace myself for day-to-day things  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5

**COGNITIVE DOMAIN**

22. Because of PBC I had to make a lot of effort to remember things  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
23. Because of PBC I had difficulty remembering things from one day to the next  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
24. My concentration span was short because of PBC  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
25. Because of PBC I had difficulty keeping up with conversations  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
26. Because of PBC I found it difficult to concentrate on anything  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
27. Because of PBC I found it difficult to remember what I wanted to do  
a. Coding: Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5

**EMOTIONAL DOMAIN**

28. Because of PBC I get more stressed about things than I used to  
a. Coding: Not at all=1, A little=2, Somewhat=3, Quite a bit=4, Very much=5
30. Having PBC gets me down  
a. Coding: Not at all=1, A little=2, Somewhat=3, Quite a bit=4, Very much=5
33. I worry about how my PBC will be in the future  
a. Coding: Not at all=1, A little=2, Somewhat=3, Quite a bit=4, Very much=5

**SOCIAL DOMAINS**

29. My sex life has been affected because of PBC  
a. Coding: Not at all=1, A little=2, Somewhat=3, Quite a bit=4, Very much=5,  
Does not apply=0
31. I feel I neglect my family because of having PBC  
a. Coding: Not at all=1, A little=2, Somewhat=3, Quite a bit=4, Very much=5,  
Does not apply=0
32. I feel guilty that I can't do what I used to do because of having PBC  
a. Coding: Not at all=1, A little=2, Somewhat=3, Quite a bit=4, Very much=5
34. I sometimes feel frustrated that I can't go out and enjoy myself  
a. Coding: Strongly disagree=1, Disagree=2, Neither=3, Agree=4, Strongly  
agree=5
35. I tend to keep the fact that I have PBC to myself  
a. Coding: Strongly disagree=1, Disagree=2, Neither=3, Agree=4, Strongly  
agree=5
36. I can't plan holidays because of having PBC  
a. Coding: Strongly disagree=1, Disagree=2, Neither=3, Agree=4, Strongly  
agree=5
37. My social life has almost stopped

- a. Coding: Strongly disagree=1, Disagree=2, Neither=3, Agree=4, Strongly agree=5
- 38. Everything in my life is affected by PBC
  - a. Coding: Strongly disagree=1, Disagree=2, Neither=3, Agree=4, Strongly agree=5
- 39. PBC has reduced the quality of my life
  - a. Coding: Strongly disagree=1, Disagree=2, Neither=3, Agree=4, Strongly agree=5
- 40. I can still lead a normal life, despite having PBC
  - a. Coding (reverse): Strongly agree=1, Agree=2, Neither=3, Disagree=4, Strongly disagree=5

**15.2 Appendix 2: PROMIS Fatigue-SF 7a**

**Please respond to each question by marking one box per row.**

**In the past 7 days...**

| Item         | Question                                                             | Never | Rarely | Sometimes | Often | Always |
|--------------|----------------------------------------------------------------------|-------|--------|-----------|-------|--------|
| FATEXP<br>20 | How often did you feel tired?                                        | 1     | 2      | 3         | 4     | 5      |
| FATEXP<br>5  | How often did you experience extreme exhaustion?                     | 1     | 2      | 3         | 4     | 5      |
| FATEXP<br>18 | How often did you run out of energy?                                 | 1     | 2      | 3         | 4     | 5      |
| FATIMP<br>33 | How often did your fatigue limit you at work (include work at home)? | 1     | 2      | 3         | 4     | 5      |
| FATIMP<br>30 | How often were you too tired to think clearly?                       | 1     | 2      | 3         | 4     | 5      |
| FATIMP<br>21 | How often were you too tired to take a bath or shower?               | 1     | 2      | 3         | 4     | 5      |
| FATIMP<br>40 | How often did you have enough energy to exercise strenuously?        | 5     | 4      | 3         | 2     | 1      |

Note: FATIMP40 is reverse-scored (5=Never, 1=Always)

**15.3 Appendix 3: Work Productivity and Activity Impairment Questionnaire****Work Productivity and Activity Impairment Questionnaire:  
Specific Health Problem V2.0 (WPAI-SHP: Primary Biliary Cholangitis)**

The following questions ask about the effect of your Primary Biliary Cholangitis on your ability to work and perform regular activities. *Please fill in the blanks or select a number, as indicated.*

1. Are you currently employed (working for pay)? \_\_\_\_\_ NO \_\_\_\_ YES  
*If NO, check "NO" and skip to question 6.*

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your Primary Biliary Cholangitis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your Primary Biliary Cholangitis. Do not include time you missed to participate in this study.*

\_\_\_\_\_ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

\_\_\_\_\_ HOURS

4. During the past seven days, how many hours did you actually work?

\_\_\_\_\_ HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your Primary Biliary Cholangitis affect your productivity while you were working?

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Primary Biliary Cholangitis affected your work only a little, choose a low number. Choose a high number if Primary Biliary Cholangitis affected your work a great deal.*

Consider only how much Primary Biliary Cholangitis affected  
productivity while you were working.

---

|                                                      |   |   |   |   |   |   |   |   |   |   |    |                                                                  |
|------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|----|------------------------------------------------------------------|
| Primary Biliary Cholangitis had no effect on my work | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Primary Biliary Cholangitis completely prevented me from working |
|------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|----|------------------------------------------------------------------|

SELECT A NUMBER

6. During the past seven days, how much did your Primary Biliary Cholangitis affect your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If Primary Biliary Cholangitis affected your activities only a little, choose a low number. Choose a high number if Primary Biliary Cholangitis affected your activities a great deal.*

Consider only how much Primary Biliary Cholangitis affected your ability to do your regular daily activities, other than work at a job.

|                                                                  |   |   |   |   |   |   |   |   |   |   |    |                                                                                    |
|------------------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|----|------------------------------------------------------------------------------------|
| Primary Biliary Cholangitis had no effect on my daily activities |   |   |   |   |   |   |   |   |   |   |    | Primary Biliary Cholangitis completely prevented me from doing my daily activities |
|                                                                  | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |                                                                                    |

SELECT A NUMBER

**15.4 Appendix 4: Worst Itch Numeric Rating Scale (WI-NRS)**

Please indicate the intensity of the worst itching you have experienced over the past 7 days:

No itching

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0 1 2 3 4 5 6 7 8 9 10Worst Itch  
Imaginable

SELECT A NUMBER