PASS INFORMATION

Title	Postauthorisation Safety Study (PASS) of Avatrombopag in Patients With Severe Chronic Liver Disease (CLD)
Protocol version identifier	Version 2.0
Date of last version of protocol	14 December 2023
EU PAS Register number	Study will be registered before start of data collection
Active substance	Avatrombopag maleate, ATC code B02BX08
Medicinal product	Doptelet
Product reference	EMEA/H/C/004722
Procedure number	EMEA/H/C/004722/MEA/002
Marketing authorisation holder(s)	Swedish Orphan Biovitrum AB (publ)
Joint PASS	No
Research question and objectives	The research question is, "Among adult patients with severe chronic liver disease (CLD) and severe thrombocytopenia initiating avatrombopag in preparation for a scheduled elective invasive procedure, what is the difference in liver function measured before and after the procedure?" The primary study objective is to estimate, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, differences between liver function test values measured before and after the elective invasive procedure, according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion). Secondary study objectives are: ▪ Describe, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, the frequency and severity of specific hepatic clinical outcomes, i.e., ascites and encephalopathy, before and after the procedure (and before and after treatment), according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion). ▪ Collect, among patients with severe CLD and severe thrombocytopenia treated with avatrombopag who are scheduled for an elective invasive procedure, adverse drug reactions attributed to avatrombopag that are recorded in the patients' medical records.
Country(-ies) of study	European countries

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Version and Date:	2.0, 14 December 2023

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2 List of Abbreviations

Abbreviation	Term
ADR	adverse drug reaction
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
CI	confidence interval
CLD	chronic liver disease
CONSORT	Consolidated Standards of Reporting Trials
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
ICMJE	International Committee of Medical Journal Editors
INR	international normalised ratio
ISPE	International Society for Pharmacoepidemiology
LFT	liver function test
MAH	marketing authorisation holder
MELD	Model of End-Stage Liver Disease
*n*Q yyyy	quarter of the calendar year
OQ	Office of Quality (RTI Health Solutions)
PASS	postauthorisation safety study
PSUR	Periodic Safety Update Report
RMP	risk management plan
SD	standard deviation
SmPC	summary of product characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TPO-RA	thrombopoietin receptor agonist

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4 Abstract

Title: Postauthorisation Safety Study (PASS) of Avatrombopag in Patients With Severe Chronic Liver Disease (CLD)

Version: 2.0, 14 December 2023

Lia Gutiérrez, BSn, MPH
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Rationale and background: Chronic liver disease (CLD) refers to a cluster of diseases with varying degrees of intrahepatic inflammatory necrosis and/or fibrosis caused by different aetiologies. Thrombocytopenia (a platelet count under 150 x 10^9/L) in patients with severe CLD results from the associated portal hypertension and low thrombopoietin levels. Avatrombopag maleate (Doptelet®) is an orally administered thrombopoietin receptor agonist (TPO-RA) approved by the European Medicines Agency (EMA) on 20 June 2019 for the treatment of severe thrombocytopenia in patients with CLD who are scheduled to undergo an elective invasive procedure. This protocol describes a postauthorisation safety study (PASS) that will address EMA's request to further characterise the safety profile of avatrombopag in relation to changes in liver function measured before and after the elective invasive procedure, in patients with severe CLD.

Research question and objectives: The research question is, "Among adult patients with severe CLD and thrombocytopenia who received avatrombopag in preparation for a scheduled elective invasive procedure, what is the difference in liver function measured before and after the procedure?"

The primary objective of the avatrombopag PASS is to estimate, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, differences between liver function test (LFT) values measured before and after the elective invasive procedure according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion).

The secondary objectives are:

- Describe, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, the frequency and severity of specific hepatic clinical outcomes, i.e., ascites and encephalopathy, before and after the procedure (and before and after treatment), according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion).
- Collect, among patients with severe CLD and severe thrombocytopenia treated with avatrombopag who are scheduled for an elective invasive procedure, adverse drug reactions (ADRs) attributed to avatrombopag that are recorded in the patients' medical records.

Study design: This will be a non-interventional, multinational descriptive cohort study conducted through secondary data collected via review of existing medical charts from patients managed in routine clinical practice at clinical sites in countries in Europe. Hospital sites in Austria, Denmark, the Netherlands, and Spain plan to participate in this study.

The study will collect patients' data from the date avatrombopag was approved for reimbursement in the targeted countries (1Q 2020) through approximately 6 years later; i.e., estimated end of study data collection in 2Q 2026. The study will also collect data from patients treated with lusutrombopag and patients receiving platelet transfusions to provide further context for the study results. No formal comparisons between the 3 study cohorts will be performed.

Population: The source population will consist of patients under the care of physicians practising at hospitals or specialised outpatient settings (hospitals or specialty clinics) in European countries, where patients are being treated for severe thrombocytopenia due to severe CLD in preparation for an elective invasive procedure.

The study population will comprise adult patients with documented severe CLD (Child-Pugh C or Model of End-Stage Liver Disease (MELD) score > 24) and severe thrombocytopenia (platelet count < 50 x 10^9/L) initiating treatment with avatrombopag or lusutrombopag or receiving a platelet transfusion in preparation for an elective invasive procedure during the study period.

Follow-up will start on the index date and end at the earliest of (1) 30 days after the date of the elective invasive procedure for patients who had a procedure within 15 days of the end of treatment or 30 days after the last date of treatment for patients who did not have a procedure within 15 days after the end of treatment, (2) death, or (3) loss to follow-up.

Variables: The exposures will be avatrombopag, lusutrombopag, and platelet transfusions ascertained from the patients' medical records.

The primary study outcome will be liver function measured through the following biochemical LFTs measured in blood before and after the elective invasive procedure as recorded in each patient's medical record: alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyltransferase, bilirubin (total and direct), albumin, and the international normalised ratio.

The secondary outcomes will include the frequency and severity of ascites and hepatic encephalopathy before and after the procedure (and before and after treatment), according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion), as recorded in the patients' medical records. Additionally, among patients treated with avatrombopag, collection of ADRs from patients' records will not involve any individual interaction with patients (secondary data collection). Any ADRs attributed to

avatrombopag that are recorded in the patients' medical records will be summarised in the study report.

Key data collected from patient medical records will include demographics, medical history of CLD, relevant comorbidities, comedications, and type of elective invasive procedure (as available).

Data sources: The source of information for this study will be the medical records of patients who meet all the inclusion criteria and none of the exclusion criteria during the study period at selected hospital sites in Austria, Denmark, the Netherlands, and Spain. Patients will be identified by participating study physicians in each country. Pseudonymised data from patients providing informed consent or non-opposition according to specific local regulatory and legal requirements will be abstracted for the study using a study-specific data collection form.

Study size: The uptake of avatrombopag among patients with severe CLD in the selected countries will be the main driver of the study size. Any patients at participating sites treated with avatrombopag or lusutrombopag or receiving a platelet transfusion who meet all eligibility criteria will be included in the study. Most participating sites have estimated that 1 to 5 potential patients will be categorised in Child-Pugh class C or have a MELD score >24 and will receive/have received avatrombopag during the study period due to the rarity of these patients undergoing elective procedures. Initial feasibility estimates indicate that approximately 30 patients with severe CLD receiving avatrombopag could be included in the study. Assuming that the true difference between LFT values measured before and after the elective invasive procedure has a distribution with a mean of 0 and a standard deviation (SD) of 0.2, the number of patients needed for a study to have an 80% probability that the upper limit of the 95% confidence interval (CI) around the estimated mean difference will be below 0.1, 0.2, and 0.3, would be 31, 9, and 4, respectively. Assuming that the SD of the pre- and postprocedure difference is 0.6, the number of patients needed would be 285, 73, and 30, respectively. This study size would be needed for each treatment group.

Data analysis: This will be a descriptive study. Characteristics of study patients—including age, sex, comorbidities, medical history of CLD, concomitant medications, and type of elective invasive procedure scheduled—will be described.

The distribution of liver function outcomes among study patients will be examined. For each study cohort, differences between LFT values measured before and after the procedure (and before and after the treatment) will be calculated with 95% CIs. Also for each study cohort, differences in the presence and severity of ascites and encephalopathy measured before and after the procedure (and before and after the treatment) will be assessed.

Among avatrombopag-treated patients, ADRs will be summarised as counts and percentages and mean time (days) from avatrombopag initiation to the date of the occurrence of the ADR.

Milestones:

- Protocol submission: 15 December 2023
- Regulatory endorsement of protocol: estimated 1Q 2024
- Progress report: estimated 2Q 2025
- Final study report: estimated 1Q 2027

5 Amendments and Updates

Protocol version 2.0 dated 14 December 2023 incorporates substantial changes based on the Pharmacovigilance Risk Assessment Committee's (PRAC's) review of protocol version 1.0 (dated 15 June 2023), documented in the PRAC Assessment Report and adopted conclusion on 10 October 2023.

Version	Date	Section(s) of study protocol	Amendment or update	Reason
2.0	11 Dec 2023	PASS Information; 4, Abstract; 8, Research Question and Objectives	Revise research question	To address PRAC's request to reformulate research question
2.0	11 Dec 2023	PASS Information; 4, Abstract; 8, Research Question and Objectives; 9.3.2, Outcomes; 9.7, Data Analysis; 9.9, Limitations; 11, Management and Reporting of Adverse Events/Adverse Reactions	Add secondary study objectives	To address PRAC's request to assess hepatic outcomes—i.e., ascites and encephalopathy—and collect information on ADRs
2.0	11 Dec 2023	4, Abstract; 6, Milestones; 9.2.3, Study Period	Delete progress report 2 and update timelines to account for anticipated PRAC protocol endorsement in 1Q 2024	To address PRAC's request to delete one progress report
2.0	11 Dec 2023	4, Abstract; 9.1, Study Design	Add rationale for inclusion of lusutrombopag and platelet transfusion cohorts	Address PRAC's request to discuss proposed study cohorts in relation to the research question
2.0	11 Dec 2023	4, Abstract; 9.2.1, Countries and Study Sites	Expand information on countries and study sites	Address PRAC's request to detail the hospitals or specialised outpatient settings included in the study
2.0	11 Dec 2023	9.2.2, Population	Add text to specify that no restrictions will be applied to the study population in relation to the performance of an elective procedure	Improve clarity
2.0	11 Dec 2023	9.2.2, Population, Figure 1	Add footnotes to Figure 1	Address PRAC's question regarding population included in a sensitivity analysis
2.0	11 Dec 2023	9.2.2, Population	Add as inclusion criterion the use of avatrombopag, lusutrombopag, or platelet transfusions	Improve clarity
2.0	11 Dec 2023	9.3.3, Covariates	Add calendar year of the index date	Add relevant covariate
2.0	11 Dec 2023	4, Abstract; 9.4, Data Sources	Expand information on study feasibility assessment	Address PRAC's request for additional information on study sites
2.0	11 Dec 2023	4, Abstract; 9.5, Study Size	Add details on study size calculations	Address PRAC's request to clarify study size calculations

Version	Date	Section(s) of study protocol	Amendment or update	Reason
2.0	11 Dec 2023	9.6, Data Management	Added text on overall data management procedures	PRAC's request to discuss further details regarding data management
2.0	11 Dec 2023	9.8, Quality Control	Added text on quality check procedures, storage and archiving of study data, and overall quality procedure of analyses	PRAC's request to clarify methods of quality assurance

ADR = adverse drug reaction; PASS = postauthorization safety study; PRAC = Pharmacovigilance Risk Assessment Committee (of the EMA).

6 Milestones and Timeline

Milestone	Actual/planned date
Protocol submission (v. 1.0)	30 June 2023 (planned)
Revised protocol submission (v. 2.0)	15 December 2023
Protocol endorsement by the EMA	Estimated 1Q 2024
Registration in EU PAS Register	No later than 6 months after EMA protocol endorsement and before the start of data collection
Start of data collection[a]	Estimated 4Q 2024
End of data collection[b]	Estimated 2Q 2026
Study progress report	Estimated 2Q 2025
Final report of study results	Estimated 1Q 2027

EMA = European Medicines Agency; EU PAS Register = European Union electronic Register of Post-Authorisation Studies; *n*Q yyyy = quarter of the calendar year.

Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

[a] Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts" (EMA, 2017b).

[b] End of data collection is "the date from which the analytical data set is completely available" (EMA, 2017b).

7 Rationale and Background

Chronic liver disease (CLD) refers to a cluster of diseases with varying degrees of intrahepatic inflammatory necrosis and/or fibrosis caused by different aetiologies with a history of at least 6 months (Zhang and Meng, 2022). The burden of CLD, usually including cirrhosis and its complications, is significant. The most common aetiologies of CLD are chronic hepatitis B virus, hepatitis C virus, alcohol-related liver disease, and non-alcoholic fatty liver disease (Moon et al., 2020). The age-adjusted prevalence of CLD in 2016 in 35 European countries for males and females ranged from 447 (Iceland) to 1,100 (Romania) cases per 100,000 (Pimpin et al., 2018).

As CLD progresses, patients develop complications of hepatocellular dysfunction and portal hypertension that contribute to liver-related morbidity and mortality (D'Amico et al., 2018). Various scoring systems are used to assess the severity and prognosis of CLD. The Child-Pugh score is a composite score of 3 laboratory-based biomarkers (albumin, bilirubin, and prothrombin time levels) and 2 clinical variables (ascites and encephalopathy). Within each variable, a score of 1 to 3 is given depending on the severity of abnormality with the final score classifying the severity of CLD into 1 of 3 Child-Pugh classes (Kok and Abraldes, 2019):

- Class A (score 5-6): well-compensated disease
- Class B (score 7-9): functional compromise
- Class C (score 10-15): decompensated disease

A second score, the Model of End-Stage Liver Disease (MELD) score 3.0 uses sex; serum measurements of bilirubin, creatinine, albumin, and sodium; and the international normalised ratio (INR) measurement in blood; patients with intermediate- or high-risk CLD have MELD scores > 24 (Kim et al., 2021). The MELD score was initially used to predict mortality within 3 months after the transjugular intrahepatic portosystemic shunt procedure and is currently used to prioritise patients for receipt of a liver transplant (Kim et al., 2021; Song et al., 2023).

7.1 Thrombocytopenia in Patients With CLD

Thrombocytopenia (a platelet count under 150 x 10^9/L) in patients with severe CLD results from the associated portal hypertension and low thrombopoietin levels. Its prevalence among patients with cirrhosis is high (up to 78%) (Brown, 2019; Miller et al., 2019). Severe thrombocytopenia (a platelet count <50,000/µL [or 50 x 10^9/L]) can contribute to an increased risk of bleeding in patients with CLD, and the availability of an effective treatment is essential for those patients requiring invasive diagnostic and therapeutic procedures (Giannini et al., 2010; Miller et al., 2019). In patients with thrombocytopenia, studies suggest that it is difficult to establish a platelet count above which the risk of bleeding would be minimal (Napolitano et al., 2017; Seeff et al., 2010).

The standard treatment of severe thrombocytopenia in patients with CLD traditionally has been platelet transfusion. However, this treatment has disadvantages, such as transfusion reactions, risk of infections, cost, short duration of effect, and diminished effectiveness over time with repeated use (Dieterich et al., 2020). Thrombopoietin receptor agonists (TPO-Ras), are drugs that stimulate proliferation and differentiation of megakaryocytes from bone marrow progenitor cells by binding to and activating the thrombopoietin receptor, resulting in increased production of platelets.

Avatrombopag maleate (Doptelet®) is an orally administered TPO-RA approved by the European Medicines Agency (EMA) on 20 June 2019 for the treatment of severe thrombocytopenia in patients with CLD who are scheduled to undergo an invasive procedure (EMA, 2020a). Its efficacy has been proven in clinical trials (Bussel et al., 2014; Jurczak et al., 2018; Kuter and Allen, 2018; Li et al., 2019; Michelson et al., 2018; Terrault et al., 2018). In January 2021, avatrombopag was also approved by the EMA for the treatment of primary chronic immune thrombocytopenia in adult patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins) (EMA, 2020b). Another TPO-RA, lusutrombopag (Mulpleo®), was approved by the EMA in February 2019 for the treatment of severe thrombocytopenia in adult patients with CLD undergoing invasive procedures. The advantage of avatrombopag and lusutrombopag is their effectiveness in increasing platelet counts (Brown, 2019; Miller et al., 2019) and reducing the need for platelet transfusions in connection with invasive procedures.

7.2 Risk of Worsening of Hepatic Function in Patients With CLD

In the pivotal phase 3 trials of avatrombopag in patients with CLD, the overall incidence of hepatic-related events was comparable to placebo; however, the safety of avatrombopag in patients with severe hepatic impairment (Child-Pugh class C, MELD score > 24) could not be established due to the small numbers (less than 6%) of patients with severe liver disease (Child-Pugh class C) enrolled in these trials as elective invasive procedures are often avoided in this population (Terrault et al., 2018). As described in the product information, avatrombopag should be used in such patients only if the expected benefit outweighs the expected risks (Doptelet SmPC, 2022).

Among patients with severe CLD, it may be difficult to predict changes in liver function that are purely related to disease progression over even short periods of time (D'Amico et al., 2014; Li et al., 2018). Although there is no evidence that an elective invasive procedure increases the risk of hepatic decompensation or worsening of liver function, some specific surgeries such as abdominal in general (especially if ascites is present) and hepatobiliary more specifically are associated with increased morbidity and mortality among patients with severe CLD. There is also consensus that emergency surgery is associated with more complications than elective surgery (Endale Simegn et al., 2022; Friedman, 1999; Muilenburg et al., 2009).

7.3 Rationale for the Avatrombopag PASS

In June 2019, as part of the initial authorisation procedure, the EMA asked Swedish Orphan Biovitrum AB (Sobi), the marketing authorisation holder (MAH) of avatrombopag in the European Union, *"to conduct a post-authorisation safety study (PASS) to better understand the safety of avatrombopag in patients with Child-Pugh class C liver disease or MELD scores > 24. Notably to further characterise the following safety concerns: 'Hepatic worsening function in patient with Child-Pugh class C' and 'Use in patients with MELD scores > 24.' This PASS was included in the RMP as a category 3 study within the additional PhV activities."* (Sobi data on file, 2022)

The MAH has since then submitted to the EMA several feasibility study protocols and feasibility study reports evaluating potential data sources in the United States and in countries in Europe that involved different study designs and analysis approaches. In January 2023, while acknowledging the limitations encountered for conducting a PASS as documented through the multiple study feasibility evaluations, the EMA Pharmacovigilance Risk Assessment Committee assessor considered that "*routine pharmacovigilance activities will be not sufficient for further characterization of the safety profile of avatrombopag in subjects with severe CLD and the MAH should submit a PASS protocol using medical chart review as study design. The study should take into account differences between pre- and post-procedural liver functions test with 95% confidence intervals [CIs] and Paired t-test to determine statistical significance with 0.05 (two-tailed) as the level of statistical significance. This should be performed separately for the avatrombopag, platelet and lusutrombopag groups*." (Sobi data on file, 2023)

This protocol describes a PASS of avatrombopag in patients with severe CLD (defined as Child-Pugh class C or MELD scores > 24) and thrombocytopenia to characterise changes in liver function test (LFT) results before and after an elective invasive procedure according to the treatment received before the elective invasive procedure. It follows the structure and contents as included in the EMA's *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII—Post-Authorisation Safety Studies* (EMA, 2017b).

8 Research Question and Objectives

The research question is, "Among adult patients with severe CLD and severe thrombocytopenia who received avatrombopag in preparation for a scheduled elective invasive procedure, what is the difference in liver function measured before the procedure and after the procedure?"

The primary study objective is to estimate, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, differences between LFT values measured before and after the elective invasive procedure, according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion).

The secondary study objectives are:

- Describe, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, the frequency and severity of specific hepatic clinical outcomes, i.e., ascites and encephalopathy, before and after the procedure (and before and after treatment), according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion).
- Collect, among patients with severe CLD and severe thrombocytopenia treated with avatrombopag who are scheduled for an elective invasive procedure, adverse drug reactions (ADRs) attributed to avatrombopag that are recorded in the patients' medical records.

The rationale for the inclusion of patients treated with lusutrombopag or platelet transfusion is described in Section 9.1.

9 Research Methods

9.1 Study Design

This will be a non-interventional, multinational descriptive cohort study using secondary data collected via review of existing medical charts from patients managed in routine clinical practice at hospital sites in countries in Europe. The study will be conducted at approximately 10 to 15 clinical sites in selected European countries managing adult patients with severe CLD and severe thrombocytopenia who initiate avatrombopag or lusutrombopag, or who receive a platelet transfusion, in preparation for an elective invasive procedure. The cohorts of patients treated with lusutrombopag and patients receiving a platelet transfusion will provide further context for the results of the Avatrombopag Cohort. The design of the study is descriptive; therefore, no formal comparative analyses between the 3 study cohorts will be performed.

9.2 Setting

The study will be conducted in hospital or specialised outpatient settings (hospitals or specialty clinics) where patients with severe CLD and thrombocytopenia are treated in preparation for an elective invasive procedure.

At each site, a study investigator will be identified to facilitate collection of patients' data from medical records and, as needed, support the ethics committee submission as required by local policies. Access to data from both hospital and outpatient/primary care settings would be desirable if postprocedure or posttreatment follow-up visits and laboratory test monitoring occur in a different healthcare setting (e.g., primary care).

9.2.1 Countries and Study Sites

Countries with reimbursement approval of both avatrombopag and lusutrombopag for the CLD indication were considered for this study. The following sites in European countries plan to participate in this study. This should allow for inclusion of a representative sample of European patients.

Austria

- Klinikum Klagenfurt, Vienna

Denmark

- Hvidovre Hospital, Copenhagen

The Netherlands

- Erasmus Medical Center, Rotterdam

Spain

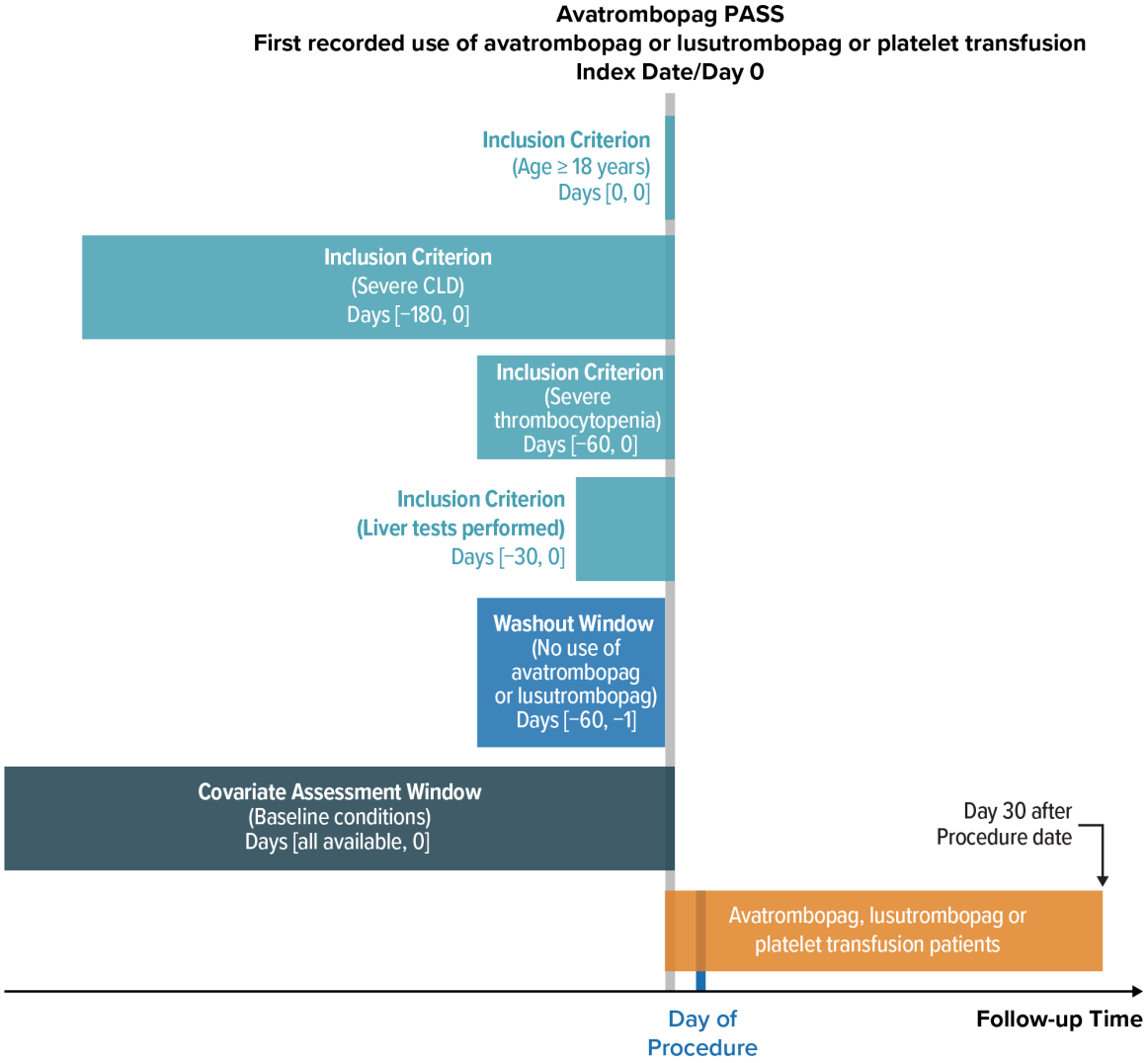
- Hospital Universitario Puerta de Hierro, Madrid
- Hospital Universitario de la Plana, Villareal, Castellón
- Hospital Universitario Miguel Servet, Zaragoza
- Hospital Universitario Insular de Gran Canaria, Las Palmas

9.2.2 Population

The study population will comprise patients initiating treatment with avatrombopag or lusutrombopag, or receiving a platelet transfusion, in preparation for an elective invasive procedure during the study period (see Section 9.2.4). To avoid introducing a potential selection bias, no restrictions will be applied to the study population in relation to whether the elective procedure was performed. At each participating site, all patients meeting the eligibility criteria detailed later in this section will be included in the study.

The study cohorts, with the timing for assessment of baseline covariates and the follow-up period, are shown in Figure 1.

Figure 1. Study Cohorts: Overview of the Timing for Covariate Ascertainment



CLD = chronic liver disease; PASS = postauthorisation safety study.

Note: Patient informed consent for accessing patients' records will be obtained as required by local regulations.

Note: For patients receiving platelet transfusion, the index date and procedure date will be the same date if the platelet transfusion occurs on the date of the elective procedure. If so, this date will be also the start of the postprocedure period.

Note: Assessment of eligibility criteria, treatment start (for each study cohort), and start of follow-up will occur at the index date. The figure depicts follow-up for patients who undergo a procedure (primary objective/main analysis)

Note: For patients who do not have a procedure performed (sensitivity analysis, not depicted in the figure), follow-up will end 30 days after the last day of treatment.

Source: Template for figure from Schneeweiss et al. (2019).

Patients meeting the following inclusion criteria and none of the exclusion criteria at the index date/day 0 will be included in the study. Index date/day 0 is the day of first eligible avatrombopag or lusutrombopag treatment or day of platelet transfusion.

Inclusion criteria:

- Recorded use of avatrombopag, lusutrombopag, or platelet transfusion on the index date for a planned elective procedure
- 18 years of age or older
- A score indicating severe CLD within 180 days before and including the index date
  - Child-Pugh class C (score 10-15): decompensated disease; OR
  - MELD score >24: intermediate risk or high risk
- Laboratory values compatible with severe thrombocytopenia ($<50 \times 10^9$/L) in the 60 days before and including the index date
- Written informed consent or non-opposition according to the specific local regulatory and legal requirements, obtained before accessing the patients' medical records if required by local regulations
- LFT results recorded within 30 days before and including the index date

Exclusion criterion:

- Treatment with avatrombopag or lusutrombopag within the 60 days before the index date.

  Note: Due to its transient effect, up to 72 hours, patients receiving platelet transfusions before the index date will not be excluded (Sahota et al., 2011).

9.2.3 Study Period

The study will collect patients' data from the date avatrombopag was approved for reimbursement in the targeted countries (1Q 2020) through approximately 6 years later; i.e., estimated end of study data collection in June 2026.

9.2.4 Follow-up

Follow-up will start on the index date/day 0 and end at the earliest of (1) 30 days after the date of the elective invasive procedure for patients who had a procedure within 15 days of the end of treatment or 30 days after the last date of treatment for patients who did not have a procedure within 15 days after the end of treatment, (2) death, or (3) loss to follow-up. Those patients who undergo a procedure 16 to 30 days after completing the treatment will be counted, and this count will be reported, but they will not be included in any further analysis.

9.3 Variables

9.3.1 Exposure

The exposures will be avatrombopag, lusutrombopag, and platelet transfusions ascertained from the patients' existing medical records. Patients meeting the eligibility criteria may be included more than once if they have more than 1 exposure for different elective procedures during the study period.

9.3.1.1 Avatrombopag Cohort

At each clinical site, eligible patients with a recorded use of avatrombopag meeting the eligibility criteria (Anatomical Therapeutic Chemical [ATC] code: B02BX08) within the study period will be assigned to the Avatrombopag Cohort. The recommended daily dose of avatrombopag in CLD is based on the patient's platelet count (see Table 1). According to the dosing recommendations, patients should undergo their procedure 5 to 8 days after the last dose of avatrombopag (Doptelet SmPC, 2022).

Information on avatrombopag daily dose, date of treatment start, and date of treatment end will be collected.

Table 1. Daily Dose Recommendation for Avatrombopag in CLD

Platelet count	Once-daily dose	Duration of dosing
<40	60 mg (three 20-mg tablets)	5 days
≥40 to <50	40 mg (two 20-mg tablets)	5 days

CLD = chronic liver disease.

9.3.1.2 Lusutrombopag Cohort

At each clinical site, eligible patients with a recorded use of lusutrombopag meeting the eligibility criteria (ATC code: B02BX07) within the study period will be assigned to the Lusutrombopag Cohort. The recommended dose of lusutrombopag in CLD is 3 mg once daily for 7 days. According to the dosing recommendations, the procedure should be performed from day 9 after the start of lusutrombopag treatment (Mulpleo SmPC, 2019). Information on lusutrombopag daily dose, date of treatment start, and date of treatment end will be collected.

9.3.1.3 Platelet Transfusion Cohort

Eligible patients with a record of receiving a platelet transfusion in preparation for an elective invasive procedure who meet the eligibility criteria within the study period will be assigned to the Platelet Transfusion Cohort. The date of the platelet transfusion will be collected for each patient.

9.3.2 Outcomes

The primary study outcome will be liver function measured through biochemical LFTs before and after the elective invasive procedure as recorded in each patient's medical record. The difference between LFT values measured before and after the procedure, i.e., preprocedure and postprocedure values, will be described according to the treatment received (see details in Section 9.7, Data Analysis). The preprocedure LFT values used for this analysis will be the measurement before and closest to the procedure date, and the postprocedure LFT values will be the last one measured after the procedure within the defined follow-up window (see details in Section 9.7, Data Analysis and Figure 2). The selected tests for assessing liver function in this study are listed in Table 2.

Table 2. Selected Liver Function Test Parameters to be Assessed in Blood

Parameter	Reference range of normal value
Alanine aminotransferase (ALT)	4-36 IU/L
Aspartate aminotransferase (AST)	5-30 IU/L
Alkaline phosphatase (ALP)	30 to 120 IU/L
Gamma-glutamyl transferase (GGT)	6-50 IU/L
Bilirubin (total)	2 to 17 µmol/L
Bilirubin (direct)	0-6 µmol/L
Albumin	35-50 g/L
International normalised ratio (INR)	1

Sources: Lala et al. (2022) and Shikdar et al. (2022).

Secondary study outcomes will include (1) ascites and encephalopathy, which are considered significant complications of CLD to be assessed in the 3 treatment cohorts, and (2) ADRs attributed to avatrombopag. The frequency and severity of ascites and hepatic encephalopathy will be described before and after the procedure (and before and after treatment), according to the treatment received, based on information recorded in patients' medical records (see details in Section 9.7, Data Analysis). Several clinical scales are available using various measures for grading ascites and hepatic encephalopathy that might be used in clinical practice (Moore and Aithal, 2006; Weissenborn, 2019). However, we propose to measure both ascites and encephalopathy following the classification of severity proposed in the Child-Pugh classification of cirrhosis (absent, slight, and moderate for ascites; none, grade 1 to 2, and grade 3 to 4 for encephalopathy) (Kok and Abraldes, 2019). We anticipate that clinical use and actual recording of any measurement tool for ascites and encephalopathy in patients' records may be limited in routine clinical practice settings (see Section 9.9, Limitations of the Research Methods).

For the ADRs outcome, the collection of ADRs from patients' records will not involve any individual interaction with patients (secondary data collection only). At each study site,

responsible study staff will collect verbatim any ADRs among avatrombopag-treated patients that are attributed to avatrombopag as recorded in the patients' medical records. Only clearly identified adverse events causally linked to avatrombopag administration as recorded in the medical records will be extracted for the purposes of this secondary outcome analysis. A diagnosis, if available, rather than individual signs and symptoms should be recorded. All collected ADRs will be coded as appropriate using the Medical Dictionary for Regulatory Activities (MedDRA) and summarised in the study report in line with EMA's reporting requirements of ADRs for non-interventional studies. No expedited reporting of ADRs or submission of individual case safety reports (ICSRs) will be required (see Section 11, Management and Reporting of Adverse Events/Adverse Reactions).

9.3.3 Covariates

The following covariates will be assessed to characterise all patients at baseline:

- **Key covariate**: Type of planned elective invasive procedure according to the risk stratification by Northup et al. (2021), as listed in Table 3.
- Whether (yes/no) procedure involved the liver or gallbladder (e.g., liver biopsy, transjugular intrahepatic portosystemic shunt, transhepatic arterial chemoembolisation or radioembolisation, cholecystostomy, or percutaneous biliary drain)
- Demographics: age, sex, country, calendar year of the index date
- Source of data: inpatient only, inpatient plus hospital outpatient/primary care, speciality clinics
- Medical history of CLD: time since first diagnosis and underlying cause(s) of CLD (alcoholic liver disease, chronic viral hepatitis, non-alcoholic steatohepatitis, genetic liver conditions [Wilson disease, alpha-1-antitrypsin deficiency, hereditary hemochromatosis], others)
- Relevant concurrent conditions associated with progression of severe CLD: hepatocellular carcinoma, bacterial infection/sepsis, gastrointestinal bleeding, surgery, and viral hepatitis comorbidity
- Child-Pugh class and/or MELD score
- Concomitant medications recorded on the index date or during a predefined lookback period, e.g., 30 days: fluvoxamine and/or ciprofloxacin and other hepatotoxic medications as listed in Annex 3
- Laboratory parameters: platelet count (most recent count before the procedure)

Table 3. Common Procedures in Patients With Cirrhosis, by Type of Procedure and Degree of Bleeding Risk

Type of procedure	Low risk	High risk
Percutaneous	▪ Paracentesis ▪ Thoracentesis ▪ Drainage catheter exchange	▪ Biliary intervention (cholecystostomy or percutaneous biliary drain) ▪ Liver biopsy ▪ Tumour ablation ▪ Non-liver intraabdominal solid-organ biopsy ▪ Intrathoracic organ biopsy ▪ Nephrostomy tube placement ▪ Central nervous system procedures ▪ Intraocular procedures/injections ▪ Intra-articular injections
Vascular	▪ Peripherally inserted central catheter line placement ▪ Central venous catheter placement ▪ Central line removal ▪ Inferior vena cava filter placement ▪ Diagnostic venography ▪ Coronary angiography and right heart catheterisation (diagnostic)	▪ Transjugular intrahepatic portosystemic shunt ▪ Angiography or venography with intervention ▪ Transjugular liver biopsy ▪ Transhepatic arterial chemoembolisation or radioembolisation ▪ Therapeutic coronary angiography
Endoscopic	▪ Diagnostic esophagogastroduodenoscopy and routine variceal band ligation ▪ Enteroscopy ▪ Colonoscopy (including mucosal biopsy) ▪ Endoscopic retrograde cholangiopancreatography without sphincterotomy ▪ Capsule endoscopy ▪ Endoscopic ultrasound without fine-needle aspiration ▪ Transesophageal echocardiogram ▪ Diagnostic bronchoscopy without biopsy	▪ Endoscopic polypectomy ▪ Endoscopic stricture dilation or mucosal resection ▪ Balloon-assisted enteroscopy ▪ Percutaneous endoscopic gastrostomy placement ▪ Endoscopic retrograde cholangiopancreatography with sphincterotomy ▪ Endoscopic ultrasound with fine-needle aspiration ▪ Cystgastrostomy ▪ Therapeutic bronchoscopy or diagnostic bronchoscopy with biopsy
Other	▪ Skin biopsy ▪ Dental cleaning and nonextraction procedures	▪ Dental extraction

Source: Northup et al. (2021).

9.4 Data Sources

The source of information for the study will be the medical records of eligible patients during the study period at the selected hospital sites in Austria, Denmark, the

Netherlands, and Spain. Specific hospital sites are listed in Section 9.2.1, Countries and Study Sites.

Sites completed feasibility questionnaires focused on the relevant available data within the medical records of patients with CLD undergoing elective procedures (liver-related laboratory test results, medication treatment records, Child-Pugh or MELD scores, adverse events), the qualifications of the site and investigator, and the availability of resources necessary for extraction of the data during the study period. Patients will be identified by participating study physicians or designated centre support personnel at each selected study site in each country. After obtaining informed consent from each patient, if required by local regulations, pseudonymised data will be collected from the patient medical records by designated centre healthcare professionals using an electronic data collection form tailored to the study objectives.

9.5 Study Size

Any patients at participating sites who meet all eligibility criteria will be included in the study. The study size estimate is based on the number of patients treated with avatrombopag, and the actual study size will be determined mainly by the overall utilisation of avatrombopag in patients with severe CLD before elective invasive procedures at the selected sites in the selected countries. At each site, all eligible patients with severe CLD treated with lusutrombopag or receiving a platelet transfusion before elective invasive procedures will be also included. Based on the study feasibility assessment, most participating sites estimated that 1 to 5 potential patients of Child-Pugh class C or MELD score >24 will receive/have received avatrombopag during the study period due to the rarity of these patients undergoing elective procedures. Based on initial feasibility estimates, it is anticipated that approximately 30 patients with severe CLD receiving avatrombopag could be included in the study. A larger number of patients who received platelet transfusions have data available at the selected sites, and very few patients are expected to have received lusutrombopag as the label includes a warning for its use in patients in Child-Pugh class C. Differences in LFT values before and after the procedure within (not between) patients exposed to avatrombopag or lusutrombopag or receiving a platelet transfusion will be estimated.

Table 4 shows the study size (for each treatment cohort) needed to have 80% probability that the upper limit of the 95% CI around the primary outcome—specifically the estimated mean difference between measurements of LFT values, taken before and after the procedure (or treatment)—will be below 0.1, 0.2, and 0.3. Calculations are based on the assumption that the true mean difference between the LFT values before and after the procedure or treatment is 0 in the population from which we are sampling. Thus, as shown in Table 4, for a standard deviation (SD) of 0.2 and upper limits of 0.1, 0.2, and 0.3, the necessary study sizes are 31, 9, and 4 respectively; for an SD of 0.6, the number of patients needed would be 285, 73, and 30, respectively. Note that the study sizes are dependent on the ratio between the SD and the upper 95% CI limits.

These study sizes would be exactly the same if both the SD and the upper limits were increased by a factor of 10 (i.e., the necessary study sizes for an SD of 2 and upper limits of 1, 2, and 3 would also be 31, 9, and 4 respectively).

Table 4. Study Size per Treatment Cohort

SD of the difference between before versus after procedure (or treatment)	Number of patients needed to have 80% probability that the upper 95% confidence limit of the mean difference is below:		
	0.1	0.2	0.3
0.2	31	9	4
0.3	73	19	8
0.4	130	31	15
0.5	200	49	21
0.6	285	73	30

SD = standard deviation.

Note: Calculations were done using Monte Carlo simulations.

9.6 Data Management

Data management and handling of data will be conducted according to a study-specific Data Management Plan (DMP), which will be finalised before the start of data collection. An electronic data capture system will be used to collect patient data. Use of electronic data capture technology minimises the burden on the physician and the centre and maximises the quality of the data while ensuring that patient privacy is maintained throughout the process. Using an electronic data capture system will improve data collection efficiency, decrease response error, and facilitate physicians' contributions.

Data collection will be performed by physicians or designated centre support staff through the abstraction of data from patient medical records directly into the electronic data capture system after written informed consent is obtained, if required according to local regulations. Before data collection begins in the study, formal training will be performed to instruct all study investigators/site support personnel on the study procedures and on procedures to be followed while entering data abstracted from medical records into the electronic data capture system. Each participating clinical site will maintain any patient-identifying information securely on site according to internal standard operating procedures or guidance documents and local regulations.

Data collection and management will be carried out using Medrio EDC, a data management system that has a secure web-based data entry interface and is fully validated and compliant with Food and Drug Administration (FDA) Information Governance standard 21 Code of Federal Regulations (CFR) Part 11, ICH Good Clinical Practices, European Union General Data Protection Regulation (EU GDPR), and HIPAA (Health Insurance Portability and Accountability Act of 1996). The Medrio system has

restricted access permissions for data entry and data management and records an audit trail of all changes to data and activity in the system in line with 21 CFR Part 11. Access to the study in Medrio will be restricted (by password protection) to only those personnel directly involved with the study, and assigned access permissions will control the level of access to that required for the role of each individual working on the study.

Source data verification will be performed on 10% of the data from each centre to monitor the accuracy and quality of the data collected. The electronic case report form will be compared with source documents by a physician or designated centre support staff who did not collect data for that patient record and using a methodology appropriate to local regulations and requirements for consent. All entries, corrections, and alterations are to be made by the responsible physician or dedicated centre support staff. Further training will be provided to personnel, if required. In addition, validation checks will be programmed within the electronic data capture system, and supplemental validation will be performed during review of the downloaded data. These steps will ensure accurate, consistent, and reliable data; data identified as erroneous or missing will be referred to the investigative site for resolution through data queries.

Appropriate data storage and archiving procedures will be followed. All study records and source documents will be retained for the maximum period required by applicable regulations and guidelines, or by institutional procedures, or for the period specified by the sponsor, whichever is longer.

9.7 Data Analysis

This section describes analyses planned and the associated planned analysis tables and figures. Shells of analysis tables are shown in Annex 4.

All individuals and their respective episodes of treatment with avatrombopag, lusutrombopag, or platelet transfusion during the study period will be identified, and the counts and percentages of those that do not meet each eligibility criterion will be described for each exposure cohort, i.e., avatrombopag, lusutrombopag, or platelet transfusion. The timing of the procedure in relation to the day of completion of treatment will also be reported (Annex 4, Analysis Table 1). Note that a single patient may be eligible to contribute more than 1 treatment episode and procedure to the analysis during the study period. Potential correlation arising from multiple procedures within an individual will be accounted for in the analysis.

The analyses will be descriptive and will be performed separately for each exposure cohort. Patients initiating avatrombopag or lusutrombopag and patients undergoing platelet transfusions will be characterised in terms of demographic and clinical characteristics such as severity of CLD and thrombocytopenia, history of previous treatments with the same indication, comorbidities, use of comedications, and type of elective invasive procedure (Annex 4, Analysis Tables 2 and 3). For continuous variables, descriptive statistics will include the mean, SD, median, first and third quartiles, and

minimum and maximum values. For categorical variables, descriptive statistics will include frequencies and percentages. For variables with missing data, the count and percentage of missingness will be reported for each variable. LFT values will be characterised by cohort and by period (Annex 4, Analysis Tables 4a-c pre- and postprocedure LFT values and Annex 4, Analysis Tables 4d-f, pre- and posttreatment LFT values). Counts and proportions of patients that do not have LFTs recorded during follow-up will be calculated.

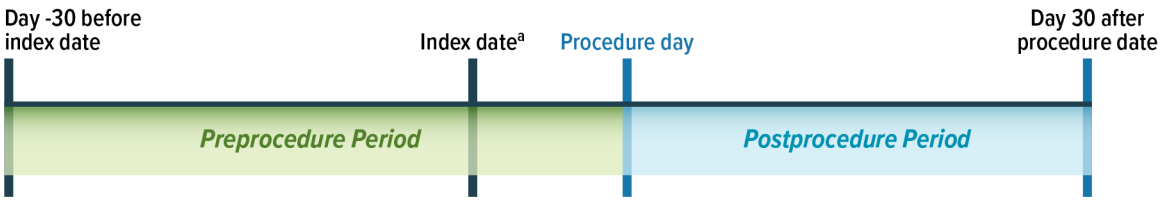
In accordance with the recommendations of the American Statistical Association, the International Committee of Medical Journal Editors (ICMJE, 2023), and expert opinion on the misuse of significance testing (Greenland et al., 2016; *Nature* editorial, 2019; Rothman and Lash, 2021), we will avoid relying on statistical significance to interpret study results. Instead of a dichotomous interpretation based on *P* values and significance testing, we will rely on a quantitative interpretation that considers the magnitude, precision, and possible bias in the estimates that we derive and report.

9.7.1 Primary Study Objective

The primary analysis linked to the primary study objective will be restricted to treatment episodes that are followed by an elective procedure within 8 days of the end of the treatment episode/platelet transfusion and focus on differences in LFT values between preprocedure and postprocedure periods. The 8-day window follows the dosing recommendations for the performance of the procedure in relation to avatrombopag treatment (Doptelet SmPC, 2022). We will assess the difference in LFT values measured before the procedure and after the procedure (postprocedure LFT values minus preprocedure LFT values) (Figure 2). The preprocedure LFT values used for this analysis will be the measurement before and closest to the procedure date, and the postprocedure LFT values will be the last values measured after the procedure within 30 days of the date of the procedure. The distribution of values in each study cohort will be examined, and the mean values along with 95% CIs and *P* values from 2-tailed paired t-tests will be reported, by cohort (Annex 4, Analysis Tables 5a-c).

As a sensitivity analysis, the primary analysis will be repeated but will include all treatment episodes that are followed by an elective procedure within 15 days of the end of the treatment instead of limiting it to 8 days (Annex 4, Analysis Table 6).

Figure 2. Difference in Liver Function Test Values Before and After a Procedure



[a] Day of first recorded use of avatrombopag or lusutrombopag or platelet transfusion.

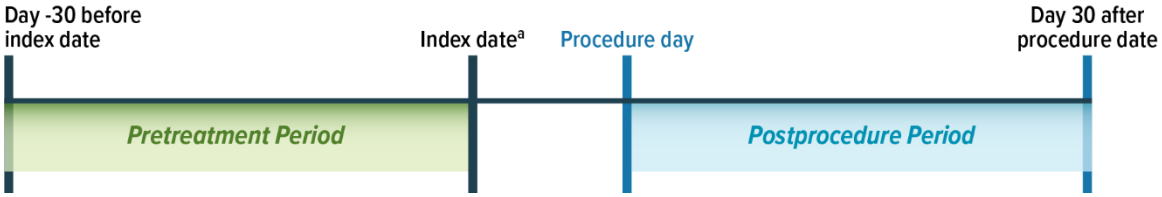
Index date and procedure date will be the same date if the platelet transfusion occurs on the date of the elective procedure. If so, this date will also be the start of the postprocedure period.

Additional analyses of the primary study objective are as follows:

- Changes in LFT values measured before the procedure and after the procedure (postprocedure LFT values minus preprocedure LFT values) in the subgroup of patients with MELD score >24, if a sufficient number of such patients are enrolled for this analysis to be meaningful.
- Changes in LFT values from before treatment, i.e., during pretreatment period, will be assessed by cohort (Annex 4, Analysis Tables 5a-c).

  For treatment episodes that had a procedure within 8 days of the end of treatment/day of platelet transfusion, the change will be calculated as postprocedure LFT value minus pretreatment LFT value; using the postprocedure LFT value nearest the end of the postprocedure period and the pretreatment LFT value nearest the index date (Figure 3).

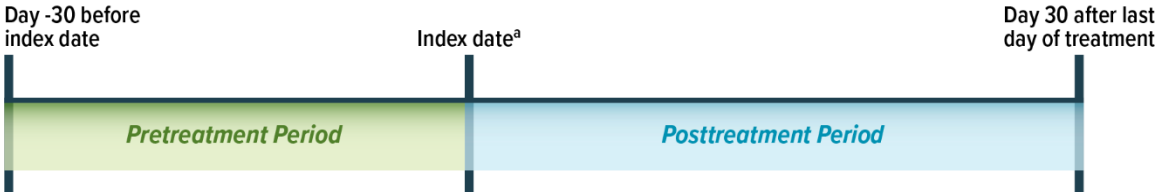
Figure 3. Difference in Liver Function Test Values Before Treatment and After Procedure in Patients Who Had a Procedure Within 8 Days of Treatment



[a] Day of first recorded use of avatrombopag or lusutrombopag or platelet transfusion.

  - For treatment episodes that are not followed by a procedure within 30 days of the end of treatment, the change/difference will be calculated as the posttreatment minus pretreatment LFT value; using the posttreatment LFT value nearest the end of the posttreatment period and the pretreatment LFT value nearest the index date (see Figure 4).
  - Note, treatment episodes that had a procedure between 9 and 30 days after the end of treatment will be excluded from these analyses.

Figure 4. Difference in Liver Function Test Values Before and After Treatment in Patients Who Did Not Have a Procedure Within 30 Days After the End of Treatment



[a] Day of first recorded use of avatrombopag or lusutrombopag or platelet transfusion.

9.7.2 Secondary Study Objective

Analyses for the secondary study objectives will focus on calculating counts and proportions of patients that have ascites and hepatic encephalopathy in each study cohort and ADRs recorded after receiving treatment with avatrombopag, as follows:

- Number and proportion of patients in each cohort with a recorded diagnosis of ascites (and by severity), before and after the procedure (and before and after treatment). The preprocedure and postprocedure periods will be defined as in the primary analysis (see Figure 2). The before and after treatment analysis will look at the number and proportion of patients with ascites, in each cohort, within 30 days of the end of the treatment. The before-treatment period will look at recorded diagnoses and severity of ascites before but closest to the first day of treatment, and the after-treatment period will focus on the earliest recorded diagnoses and severity of ascites after the last day of treatment, regardless of the date of the procedure. The after-procedure (or treatment) results will be stratified by whether a patient had ascites before the procedure (or treatment) (Annex 4, Analysis Tables 7a-c).
- Number and proportion of patients with a recorded diagnosis of hepatic encephalopathy (and by severity) before and after procedure and before and after treatment, by cohort, according to the previously defined periods before and after procedure and before and after treatment (Annex 4, Analysis Tables 8a-c).
- Changes in ascites and encephalopathy—presence or absence (and severity when the conditions are present)—over time will be displayed graphically using Sankey diagrams (Otto et al., 2022). Sankey diagrams will summarise and illustrate the proportion of patients who are in the different states of presence or absence (and severity when present) of ascites and encephalopathy before and after the procedure (and before and after the treatment) and the movement of patients between the before and after periods. Each medication-specific cohort will be displayed in separate Sankey diagrams.
- Counts and percentages of ADRs attributed to avatrombopag, among avatrombopag-treated patients, as recorded in the medical records, occurring within 30 days after the end of treatment with avatrombopag. Additionally, the mean time (days) from avatrombopag initiation to the date of the occurrence of the ADR will be also reported (Annex 4, Analysis Table 9).

9.8 Quality Control

Rigorous quality-control checks will be applied to all data collection activities and data deliverables to ensure that they are in line with applicable regulatory requirements, including local requirements. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

Physicians or designated centre support staff (data collectors) will be given detailed data collection guidelines to facilitate consistent completion of the electronic case report forms and will undertake training in the requirements per the study protocol before beginning data collection.

An initial pilot for data collection will be undertaken in at least one of the recruited study sites. The purpose of this pilot is to complete an early review of the data to check the availability and quality and to confirm the length of time required to collect the data, if suitable. Data collection guidelines and the DMP will be adjusted following the pilot, if required.

To ensure the integrity and quality of the study results, quality-checking of programs, logs, and output will be performed for accuracy of all analyses.

Standard operating procedures or internal process guidance at each clinical site will be used to guide the conduct of the study. A quality-assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

9.9 Limitations of the Research Methods

- The study will be a descriptive study and is not designed for comparisons between the treatment groups, as requested by the EMA. Patient characteristics in the 3 groups will be described.
- Maximising inclusion of patients who received avatrombopag or lusutrombopag since market availability through use of secondary data from medical records is the proposed data collection approach. However, this approach may present relevant challenges because due to the severity of the underlying liver disease, some of these patients may be deceased, and pre- and postprocedure laboratory results may have not been performed or results may be missing, which would introduce a selection bias. For clinical sites where the local regulations mandate patients' informed consent before accessing their medical records, reaching out to patients will be challenging or will not be feasible for deceased patients. Furthermore, the completeness of the records for the target exposure, outcome variables, and covariates will vary. As documented in the feasibility report of an investigator-sponsored study conducted at a clinic in Denmark (submitted under MEA procedure EMEA/H/C/004722/MEA/002.4), some patients may not attend their follow-up visit, and their postprocedure laboratory values would not be recorded. This will limit the number of evaluable patients for the assessment of differences between LFT values measured before and after the procedure. Efforts will be made to access existing medical record data from outpatient/primary care settings to complement in-hospital data.
- In patients with CLD, some of the LFT values, e.g., ALT, may vary in lower degrees of magnitude than those of patients with acute liver diseases when exposed to procedures that may potentially harm liver function. This may limit the ability to identify and measure differences in LFTs.

- Clinical use and recording in patients' records of the grading of ascites and hepatic encephalopathy may be inconsistent in routine clinical practice; important information may be missing on specific timepoints. Some patients may have an assessment of these clinical manifestations of hepatic complications before the procedure (or treatment) and not afterwards, or vice versa, and some may have no formal assessment of these clinical measures at all.
- Due to the short time (days or, for platelet transfusions, hours) between the completion of treatment and the performance of the procedure, it will be difficult to differentiate between the effect on changes in LFT values within individuals that is purely related to treatment with avatrombopag, lusutrombopag, or platelet transfusions and the effect related to the invasive procedure itself.
- The number of avatrombopag new users diagnosed with severe CLD is anticipated to be limited, which would limit the assessment of differences in liver function before and after the procedure in these patients. Also, although no between-groups comparison in the differences in liver function is planned, the limited use of lusutrombopag in Europe should also be considered. The study progress report will indicate if the anticipated study size will be reached.

9.10 Other Aspects

None.

10 Protection of Human Subjects

The proposed study is a non-interventional study using data abstracted from patient medical records. All data collected in the study will be deidentified with no breach of confidentiality regarding personal identifiers or health information. Ethics committee review and approval of the study will be obtained from each participating clinical site according to local regulations, and the requirement of informed consent or non-opposition will be followed according to the specific local regulatory and legal requirements in each country. Data protection and privacy regulations (i.e., GDPR) should be respected in collecting, forwarding, processing, and storing data from study patients.

11 Management and Reporting of Adverse Events/Adverse Reactions

Based on current guidelines from the International Society for Pharmacoepidemiology (ISPE, 2015) and the EMA *Guideline on Good Pharmacovigilance Practices (GVP): Module VI – Management and Reporting of Adverse Reactions to Medicinal Products*, Section VI:C.1.2.1 (EMA, 2017a), non-interventional studies such as the one described in this protocol, conducted using medical record reviews, do not require expedited

reporting of adverse events/reactions or submission of suspected adverse reactions in the form of ICSRs. Information on any ADRs collected during the study as part of the secondary objective will be summarised in the final study report.

12 Plans for Disseminating and Communicating Study Results

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Reports (PSURs), and other regulatory reporting requirements. Study reports will be prepared using a template following the *Guideline on Good Pharmacovigilance Practices (GVP)*, Module VIII, Section B.6.3 (EMA, 2017b).

In its *Guidelines for Good Pharmacoepidemiology Practices (GPP)*, ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE, 2015); for example, results pertaining to the safety of a marketed medication. "*…the marketing authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication*."

Study results will be published following guidelines, including those for authorship, established by the ICMJE (2023). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (von Elm et al., 2008). Although the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher et al., 2001) refers to randomised studies, it provides useful guidance applicable to non-randomised studies as well.

In alignment with the EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII: Post-Authorisation Safety Studies* (EMA, 2017b), Section VIII.B.5, and the *ENCePP Code of Conduct* (ENCePP, 2018), "the MAH and the investigator will agree upon a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments before submission of the manuscript for publication." The MAH and the research team are aware that the MAH should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication (EMA, 2017b).

13 References

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2.
ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional postauthorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Postauthorisation Safety Study (PASS) of Avatrombopag in Patients With Severe Chronic Liver Disease (CLD)

EU PAS Register® number: Study will be registered before start of data collection

Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	4; 7.3
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.3
2.1.2 The objective(s) of the study?	☒	☐	☐	4; 8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4; 9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.1; 9.9

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	4; 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	4; 9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH])	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

The study is a descriptive study and is not designed for comparisons between the treatment groups.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section number**
4.1 Is the source population described?	☒	☐	☐	4; 9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.3
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation substudy)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.7
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) an appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4; 9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation substudy)	☐	☐	☒	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQOL, QALYs, DALYS, healthcare services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.2.2; 9.9
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4; 9.3.1
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4; 9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.3.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section number**
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g., International Classification of Diseases [ICD], Medical Dictionary for Regulatory Activities [MedDRA])	☒	☐	☐	9.3.2
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.2.2; 9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation substudy, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.4; 9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	6; 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Lia Gutiérrez

Date: 14/Dec/2023

Signature: Lia Gutierrez

Electronically signed by: Lia Gutierrez
Reason: I am an authorized signatory and I approve this document.
Date: Dec 14, 2023 17:25 GMT+1

Annex 3.
List of Hepatotoxic Drugs

Hepatotoxic Drugs

Type of liver injury and pattern of test results		
Hepatocellular (elevated ALT)	**Mixed (elevated ALP + elevated ALT)**	**Cholestatic (elevated ALP + TBL)**
Acarbose	Amitriptyline	Amoxicillin–clavulanic acid
Acetaminophen	Azathioprine	Anabolic steroids
Allopurinol	Captopril	Chlorpromazine
Amiodarone	Carbamazepine	Clopidogrel
Baclofen	Clindamycin	Oral contraceptives
Bupropion	Cyproheptadine	Erythromycins
Fluoxetine	Enalapril	Estrogens
HAART drugs	Flutamide	Irbesartan
Herbals: kava and germander	Nitrofurantoin	Mirtazapine
Isoniazid	Phenobarbital	Phenothiazines
Ketoconazole	Phenytoin	Terbinafine
Lisinopril	Sulfonamides	Tricyclics
Losartan	Trazodone	
Methotrexate	Trimethoprim–sulfamethoxazole	
NSAIDs	Verapamil	
Omeprazole		
Paroxetine		
Pyrazinamide		
Rifampin		
Risperidone		
Sertraline		
Statins		
Tetracyclines		
Trazodone		
Trovafloxacin		
Valproic acid		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; HAART = highly active antiretroviral therapy; NSAID = non-steroidal anti-inflammatory drugs; TBL = total bilirubin.

Source: Navarro and Senior (2006).

Annex 4.
Shells for Analysis Tables

Analysis Table 1. Cohort Attrition

	Avatrombopag cohort	Lusutrombopag cohort	Platelet transfusion cohort
Episodes[a] of study treatment initiated during the study period	XXX	XXX	XXX
Aged 18 years or older at time treatment episode was initiated (index date)	XXX	XXX	XXX
Had severe CLD within 180 days before the index date[b]	XXX	XXX	XXX
Had severe thrombocytopenia (<50 x 10^9/L) within 60 days before the index date	XXX	XXX	XXX
Informed consent or non-opposition obtained according to local regulations	XXX	XXX	XXX
Had at least 1 LFT[c] result in the 30 days before the index date	XXX	XXX	XXX
Did not receive avatrombopag or lusutrombopag within the 90 days before the index date	XXX	XXX	XXX
Had elective procedure performed within 8 days after the end of treatment	XXX	XXX	XXX
Had elective procedure performed between 9 and 15 days after the end of treatment	XXX	XXX	XXX
Had elective procedure performed between 16 and 30 days after the end of treatment[d]	XXX	XXX	XXX
Did not have elective procedure within 30 days of the end of treatment	XXX	XXX	XXX

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CLD = chronic liver disease; GGT = gamma-glutamyl transferase; LFT = liver function test; MELD = Model for End-Stage Liver Disease.

[a] An individual patient can contribute more than 1 episode, either if they have multiple episodes within a treatment cohort or if they contribute episodes to more than one treatment cohort.

[b] Child-Pugh Class C (score 10-15) or MELD score >24.

[c] ALT, AST, ALP, GGT, total bilirubin, or direct bilirubin.

[d] Beyond enumerating the number of episodes that fall in this category, these episodes will not be included in any of the analyses.

Analysis Table 2. Baseline Characteristics

Characteristic[a]	Avatrombopag cohort (N=XXX)	Lusutrombopag cohort (N=XXX)	Platelet transfusion cohort (N=XXX)
Age in years			
Mean (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, Max	X, X, X, X, X	X, X, X, X, X	X, X, X, X, X
Missing, n (%)	X (X.X)	X (X.X)	X (X.X)
Sex, n (%)	X (X.X)	X (X.X)	X (X.X)
Male	X (X.X)	X (X.X)	X (X.X)
Female	X (X.X)	X (X.X)	X (X.X)
Missing	X (X.X)	X (X.X)	X (X.X)
Country, n (%)			
Country A	X (X.X)	X (X.X)	X (X.X)
Country B	X (X.X)	X (X.X)	X (X.X)
…			
Source of data, n (%)			
Inpatient only	X (X.X)	X (X.X)	X (X.X)
Inpatient plus hospital outpatient/primary care	X (X.X)	X (X.X)	X (X.X)
Speciality clinics	X (X.X)	X (X.X)	X (X.X)
Years since first diagnosis of CLD			
Mean (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X, X, X, X, X	X, X, X, X, X	X, X, X, X, X
Missing, n (%)	X (X.X)	X (X.X)	X (X.X)
Underlying causes of CLD, n (%)			
Alcoholic liver disease	X (X.X)	X (X.X)	X (X.X)
Chronic viral hepatitis	X (X.X)	X (X.X)	X (X.X)
Non-alcoholic steatohepatitis	X (X.X)	X (X.X)	X (X.X)
Genetic liver conditions [Wilson disease, alpha-1-antitrypsin deficiency, hereditary hemochromatosis]	X (X.X)	X (X.X)	X (X.X)
Other	X (X.X)	X (X.X)	X (X.X)
Missing	X (X.X)	X (X.X)	X (X.X)

Relevant concurrent conditions associated with progression of severe CLD, n (%)			
Hepatocellular carcinoma	X (X.X)	X (X.X)	X (X.X)
Bacterial infections/sepsis	X (X.X)	X (X.X)	X (X.X)
Gastrointestinal bleeding	X (X.X)	X (X.X)	X (X.X)
Surgery	X (X.X)	X (X.X)	X (X.X)
Viral hepatitis comorbidities	X (X.X)	X (X.X)	X (X.X)
Child-Pugh score, mean (SD)	X (X.X)	X (X.X)	X (X.X)
MELD score, mean (SD)	X (X.X)	X (X.X)	X (X.X)
Concomitant medications at procedure date			
Fluvoxamine and/or ciprofloxacin	X (X.X)	X (X.X)	X (X.X)
[Use of any drug listed in annex 3 of the protocol will be assessed]	X (X.X)	X (X.X)	X (X.X)
Not applicable, did not have a procedure	X (X.X)	X (X.X)	X (X.X)
Platelet count			
Most recent on or before index date			
Mean (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X, X, X, X, X	X, X, X, X, X	X, X, X, X, X
Missing, n (%)	X (X.X)	X (X.X)	X (X.X)
Most recent on or before procedure date			
Mean (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X, X, X, X, X	X, X, X, X, X	X, X, X, X, X
Missing, n (%)	X (X.X)	X (X.X)	X (X.X)
Not applicable, did not have a procedure, n (%)	X (X.X)	X (X.X)	X (X.X)

CLD = chronic liver disease; max = maximum; MELD = Model for End-Stage Liver Disease; Min = minimum, Q1 = first quartile, Q3 = third quartile; SD = standard deviation.

Note: Numbers (N) for each cohort refer to number of episodes, not number of patients.

[a] All characteristics are relative to index date unless otherwise noted.

Analysis Table 3. Type of Invasive Procedure Performed, by Cohort

	Avatrombopag cohort (N=XXX) n (%)	Lusutrombopag cohort (N=XXX) n (%)	Platelet transfusion cohort (N=XXX) n (%)
Type of invasive procedure[a]			
Percutaneous, low risk	X (X.X)	X (X.X)	X (X.X)
Percutaneous, high risk	X (X.X)	X (X.X)	X (X.X)
Vascular, low risk	X (X.X)	X (X.X)	X (X.X)
Vascular, high risk	X (X.X)	X (X.X)	X (X.X)
Endoscopic, low risk	X (X.X)	X (X.X)	X (X.X)
Endoscopic, high risk	X (X.X)	X (X.X)	X (X.X)
Other, low risk	X (X.X)	X (X.X)	X (X.X)
Other, high risk	X (X.X)	X (X.X)	X (X.X)
Liver or gallbladder procedure	X (X.X)	X (X.X)	X (X.X)

[a] Procedures are limited to those that occur within 8 days of the end of treatment.

Analysis Table 4a. Laboratory Test Values During Study Periods Among Patients Who Underwent a Procedure,[a] Avatrombopag Cohort

Analysis Table 4b. Laboratory Test Values During Study Periods Among Patients Who Underwent a Procedure,[a] Lusutrombopag Cohort

Analysis Table 4c. Laboratory Test Values During Study Periods Among Patients Who Underwent a Procedure,[a] Platelet Transfusion Cohort

	Preprocedure period	Postprocedure period
Total episodes, N (%)	X (100%)	X (100%)
Alanine aminotransferase (ALT)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Aspartate aminotransferase (AST)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Alkaline phosphatase (ALP)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Gamma-glutamyl transferase (GGT)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X, X, X, X, X	X, X, X, X, X
Bilirubin (total)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Bilirubin (direct)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
International normalized ratio (INR)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Albumin		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X

LFT = liver function test; max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

Note: The preprocedure LFT values used for this analysis were the measurement before and closest to the procedure date, and the postprocedure LFT values were the last values measured during the postprocedure period.

[a] Limited to episodes where procedure was performed within 8 days of the end of treatment.

Analysis Table 4d. Laboratory Test Values During Study Periods Among Patients Who Did Not Undergo a Procedure,[a] Avatrombopag Cohort

Analysis Table 4e. Laboratory Test Values During Study Periods Among Patients Who Did Not Undergo a Procedure,[a] Lusutrombopag Cohort

Analysis Table 4f. Laboratory Test Values During Study Periods Among Patients Who Did Not Undergo a Procedure,[a] Platelet Transfusion Cohort

	Pretreatment period	Posttreatment period
Total episodes, N (%)	X (100%)	X (100%)
Alanine aminotransferase (ALT)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Aspartate aminotransferase (AST)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Alkaline phosphatase (ALP)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Gamma-glutamyl transferase (GGT)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X, X, X, X, X	X, X, X, X, X
Bilirubin (total)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Bilirubin (direct)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
International normalized ratio (INR)		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X
Albumin		
Episodes with a measurement, n (%)	X (X.X)	X (X.X)
Mean (SD)	X.X (X.X)	X.X (X.X)
Min, Q1, median, Q3, max	X.X	X.X

LFT = liver function test; max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

Note: The pretreatment LFT values used for this analysis were the measurement before and closest to the procedure date, and the posttreatment LFT values were the last values measured during the posttreatment period.

[a] Limited to episodes where no procedure was performed within 30 days of the end of treatment.

Analysis Table 5a. Change in Laboratory Test Values Between the Timepoints, Avatrombopag Cohort
Analysis Table 5b. Change in Laboratory Test Values Between the Timepoints, Lusutrombopag Cohort
Analysis Table 5c. Change in Laboratory Test Values Between the Timepoints, Platelet Transfusion Cohort

	Change from before to after procedure[a]	Change from before treatment to after procedure[a]	Change from before treatment to after treatment[b]
Total episodes, N (%)	X (100%)	X (100%)	X (100%)
Alanine aminotransferase (ALT)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX
Aspartate aminotransferase (AST)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX
Alkaline phosphatase (ALP)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX
Gamma-glutamyl transferase (GGT)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX
Bilirubin (total)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
P value[c]	X.X - X.X	X.X - X.X	X.X - X.X
P value	0.XX	0.XX	0.XX

Bilirubin (direct)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX
International normalized ratio (INR)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX
Albumin			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX

CI = confidence interval; SD = standard deviation.

[a] Limited to episodes where procedure was performed within 8 days of the end of treatment.

[b] Limited to episodes where no procedure was performed within 30 days of the end of treatment.

[c] *P* values are from two-tailed paired t-test.

Analysis Table 6. Change in Laboratory Test Values Between Pre- and Postprocedure Periods Allowing up to 15 Days Between End of Treatment and Procedure, by Cohort

	Cohort		
	Avatrombopag	**Lusutrombopag**	**Platelet transfusion**
Total episodes, N (%)	X (100%)	X (100%)	X (100%)
Alanine aminotransferase (ALT)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value	0.XX	0.XX	0.XX
Aspartate aminotransferase (AST)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value	0.XX	0.XX	0.XX
Alkaline phosphatase (ALP)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value	0.XX	0.XX	0.XX
Gamma-glutamyl transferase (GGT)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value	0.XX	0.XX	0.XX
Bilirubin (total)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value	0.XX	0.XX	0.XX
Bilirubin (direct)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)

Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value	0.XX	0.XX	0.XX
International normalized ratio (INR)			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX
Albumin			
Episodes with a measurement at both points, n (%)	X (X.X)	X (X.X)	X (X.X)
Mean change (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
95% CI	X.X - X.X	X.X - X.X	X.X - X.X
P value[c]	0.XX	0.XX	0.XX

CI = confidence interval; SD = standard deviation.

Note: *P* values are from two-tailed paired t-tests.

Analysis Table 7a. Change in Ascites Grade From Before to After Procedure and From Before to After Treatment, Avatrombopag Cohort

Analysis Table 7b. Change in Ascites Grade From Before to After Procedure and From Before to After Treatment, Lusutrombopag Cohort

Analysis Table 7c. Change in Ascites Grade From Before to After Procedure and From Before to After Treatment, Platelet Transfusion Cohort

Ascites before timepoint being assessed	Ascites after timepoint being assessed	Timepoint being assessed	
		Procedure N[a] = XX n (%)	Treatment N[b] = XX n (%)
No ascites		X (X/N)	X (X/N)
	No ascites	Y (Y/X)	Y (Y/X)
	Grade 1	Y (Y/X)	Y (Y/X)
	Grade 2	Y (Y/X)	Y (Y/X)
	Grade 3	Y (Y/X)	Y (Y/X)
Grade 1		X (X/N)	X (X/N)
	No ascites	Y (Y/X)	Y (Y/X)
	Grade 1	Y (Y/X)	Y (Y/X)
	Grade 2	Y (Y/X)	Y (Y/X)
	Grade 3	Y (Y/X)	Y (Y/X)
Grade 2		X (X/N)	X (X/N)
	No ascites	Y (Y/X)	Y (Y/X)
	Grade 1	Y (Y/X)	Y (Y/X)
	Grade 2	Y (Y/X)	Y (Y/X)
	Grade 3	Y (Y/X)	Y (Y/X)
Grade 3		X (X/N)	X (X/N)
	No ascites	Y (Y/X)	Y (Y/X)
	Grade 1	Y (Y/X)	Y (Y/X)
	Grade 2	Y (Y/X)	Y (Y/X)
	Grade 3	Y (Y/X)	Y (Y/X)

Note: the denominators for the "after timepoint being assessed" rows within each of the 4 sections of the table will be the count in the "before timepoint being assessed" row (e.g., for the first section, the denominators will be the count of patients with no ascites before the procedure).

[a] Total count with ascites assessed before and after the procedure.

[b] Total count with ascites assessed before and after treatment.

Analysis Table 8a. Change in Hepatic Encephalopathy Stage Between Before and After Procedure and Between Before and After Treatment, Avatrombopag Cohort

Analysis Table 8b. Change in Hepatic Encephalopathy Stage Between Before and After Procedure and Between Before and After Treatment, Lusutrombopag Cohort

Analysis Table 8c. Change in Hepatic Encephalopathy Stage Between Before and After Procedure and Between Before and After Treatment, Platelet Transfusion Cohort

Hepatic encephalopathy stage before timepoint being assessed	Hepatic encephalopathy stage after timepoint being assessed	Timepoint being assessed	
		Procedure N[a] = XX n (%)	Treatment N[b] = XX n (%)
No hepatic encephalopathy		X (X/N)	X (X/N)
	None	Y (Y/X)	Y (Y/X)
	Stage 0	Y (Y/X)	Y (Y/X)
	Stage 1	Y (Y/X)	Y (Y/X)
	Stage 2	Y (Y/X)	Y (Y/X)
	Stage 3	Y (Y/X)	Y (Y/X)
	Stage 4	Y (Y/X)	Y (Y/X)
Stage 0		X (X/N)	X (X/N)
	None	Y (Y/X)	Y (Y/X)
	Stage 0	Y (Y/X)	Y (Y/X)
	Stage 1	Y (Y/X)	Y (Y/X)
	Stage 2	Y (Y/X)	Y (Y/X)
	Stage 3	Y (Y/X)	Y (Y/X)
	Stage 4	Y (Y/X)	Y (Y/X)
Stage 1		X (X/N)	X (X/N)
	None	Y (Y/X)	Y (Y/X)
	Stage 0	Y (Y/X)	Y (Y/X)
	Stage 1	Y (Y/X)	Y (Y/X)
	Stage 2	Y (Y/X)	Y (Y/X)
	Stage 3	Y (Y/X)	Y (Y/X)
	Stage 4	Y (Y/X)	Y (Y/X)
Stage 2		X (X/N)	X (X/N)
	None	Y (Y/X)	Y (Y/X)
	Stage 0	Y (Y/X)	Y (Y/X)
	Stage 1	Y (Y/X)	Y (Y/X)
	Stage 2	Y (Y/X)	Y (Y/X)
	Stage 3	Y (Y/X)	Y (Y/X)
	Stage 4	Y (Y/X)	Y (Y/X)
Stage 3		X (X/N)	X (X/N)
	None	Y (Y/X)	Y (Y/X)
	Stage 0	Y (Y/X)	Y (Y/X)

	Stage 1	Y (Y/X)	Y (Y/X)
	Stage 2	Y (Y/X)	Y (Y/X)
	Stage 3	Y (Y/X)	Y (Y/X)
	Stage 4	Y (Y/X)	Y (Y/X)
Stage 4		X (X/N)	X (X/N)
	None	Y (Y/X)	Y (Y/X)
	Stage 0	Y (Y/X)	Y (Y/X)
	Stage 1	Y (Y/X)	Y (Y/X)
	Stage 2	Y (Y/X)	Y (Y/X)
	Stage 3	Y (Y/X)	Y (Y/X)
	Stage 4	Y (Y/X)	Y (Y/X)

Note: the denominators for the "after timepoint being assessed" rows within each of the 6 sections of the table will be the count in the "before timepoint being assessed" row (e.g., for the first section, the denominators will be the count of patients with no hepatic encephalopathy before the procedure).

[a] Total count with hepatic encephalopathy assessed before and after the procedure.

[b] Total count with hepatic encephalopathy assessed before and after treatment.

Analysis Table 9. Adverse Drug Reactions Occurring Between Avatrombopag Treatment Initiation and 30 Days After Discontinuation, Avatrombopag-Treated Patients

MedDRA preferred term code Number (%)	Mean day relative to avatrombopag initiation[a]
X (%)	X
X (%)	X
X (%)	X
…	…
…	…
…	…
…	…
…	...

MedDRA = Medical Dictionary for Regulatory Activities.

[a] Avatrombopag initiation date is day 0.

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Final Audit Report 2023-12-14

Created:	2023-12-14
By:	Grant Stafford (gstafford@rti.org)
Status:	Signed
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