Module 1.8.2

European Union Risk Management Plan (EU-RMP) for [LYNAVOY] (linerixibat)

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Not applicable

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASBT	Apical sodium/bile salt transporter
AST	Aspartate Aminotransferase
BID	Twice Daily
CDP	Clinical Development Program
DDI	Drug-Drug Interaction
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
GI	Gastrointestinal
GLIMMER	Study 201000; GSK2330672 triaL of IBAT inhibition with Multidose Measurement for Evaluation of Response
GLISTEN	Study 212620; Global Linerixibat Itch STudy of Efficacy and Safety iN PBC
HBV	Hepatitis B Infection
HCV	Hepatitis C Infection
HI	Hepatic Impairment
HIV	Human Immunodeficiency Virus
HSP	Hepatic Safety Panel
IBAT	Ileal Bile Acid Transporter
IL-31	Interleukin-31
LLSAT	Study 212358: Long term safety and tolerability
LOF	Lack Of Function
LPA	Lysophosphatidic acid
MAP	Mean arterial pressure
MARS	Molecular Absorbance Recirculating System
OCA	Obeticholic Acid
PBC	Primary Biliary Cholangitis
PK	Pharmacokinetic
PPAR	Peroxisome proliferator-activated receptor
PSC	Primary Sclerosing Cholangitis
PV	Pharmacovigilance

PY	Person-years
QD	Once Daily
QoL	Quality of life
RMP	Risk Management Plan
SAE	Serious Adverse Event
SMQ	Standardised MedDRA Query
TB	Total Bilirubin
UDCA	Ursodeoxycholic acid
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
WOCBP	Woman of Childbearing Potential

Trademark Information

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LYNAVOY

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) (INN or common name)	Linerixibat
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Bile and liver therapy, other drugs for bile therapy. ATC code: A05AX08
Marketing Authorization Holder/ Applicant	GlaxoSmithKline Trading Services Limited
Medicinal products to which this RMP refers	Linerixibat
Invented name(s) in the European Economic Area (EEA)	LYNAVOY
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Inhibitor of the ileal bile acid transporter (IBAT), also known as the apical sodium/bile salt transporter (ASBT) or SLC10A2. The molecular formula of linerixibat is C28H38N2O7S with a molecular weight of 546.68 g/mol. Linerixibat has the chemical name 3-((((3R,5R)-3-butyl-3-ethyl-7-methyloxy-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]thiazepin-8-yl)methyl)amino)pentanedioic acid.
	Summary of mode of action Linerixibat is a reversible inhibitor of the ileal bile acid transporter. It decreases the reabsorption of bile acids in the ileum leading to their increased fecal elimination. Cholestatic pruritus is common in patients with primary biliary cholangitis (PBC), though the pathophysiology of pruritus in patients with PBC is not completely understood. Linerixibat improves pruritus in PBC patients through inhibition of IBAT as observed by a decrease in mediators of pruritus including serum bile acids, lysophosphatidic acid (LPA) [via measurement of autotaxin as a surrogate] and interleukin 31 (IL-31).

	Important information about its composition: The active substance is linerixibat. Tablet core: Microcrystalline Cellulose, Croscarmellose Sodium, Magnesium Stearate. Film coating: Hypromellose, titanium dioxide, macrogol, iron oxide black, iron oxide red.
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD).
Indication(s) in the EEA	Current (if applicable): LYNAVOY is indicated for the treatment of cholestatic pruritus in adult patients with PBC.
	Proposed (if applicable): NA
Dosage in the EEA	Current (if applicable): The recommended dosage of linerixibat is 40 mg twice daily (BID). Alternative treatment should be considered in patients for whom no treatment benefit can be established following 3 months of continuous daily treatment with linerixibat.
	Proposed (if applicable): NA
Pharmaceutical form(s) and strengths	Current (if applicable): Purple, round, biconvex film-coated tablets. Each tablet contains 40 mg of linerixibat.
	Proposed (if applicable): NA
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Treatment of cholestatic pruritus in patients with primary biliary cholangitis (PBC)

Incidence

The annual incidence of PBC from published studies globally ranges from 0.5 to 5.4 per 100,000 person-years [Colapietro, 2022]. In a 2021 meta-analysis, the pooled annual incidence from 2011 to 2020 varied across geographical region and was highest in North America (2.95 per 100,000 person-years) followed by Europe (2.61 per 100,000 person-years), and then Asia-Pacific (0.86 per 100,000 person-years) [Lv, 2021]. To our knowledge, few studies have described the incidence of pruritus in patients with PBC; this is likely because pruritus affects the majority of patients with PBC [Hegade, 2019; Mayo, 2023, Veer, 2023, Gungabissoon 2024], is chronic in nature [Hegade, 2019], and may precede the diagnosis of PBC [Jones, 2018].

Prevalence

The prevalence of PBC from published studies globally ranges from 4.8 to 41.0 per 100,000 persons [Colapietro, 2022]. In a 2021 meta-analysis, the pooled prevalence from 2011 to 2020 was highest in North America (29.9 per 100,000 persons) followed by Europe (17.3 per 100,000 persons) and then the Asia-Pacific region (15.3 per 100,000 persons) [Lv, 2021]. Additionally, a recent systematic review and meta-analysis reported the pooled prevalence to be 22.3 per 100,000 person [Gazda, 2021]. Country-specific studies from across Europe report a prevalence of PBC of 20 to 40 per 100,000 persons [Dahlqvist 2016; Sebode 2020; Marzioni 2018; de Veer 2024; Örnolfsson, 2018].

Table 2 shows the percentage of PBC patients with pruritus at any given point in time is estimated to be 55% to 89% in real-world studies [Hegade, 2019; Mayo, 2023; Veer, 2023; Gungabissoon 2024]. Observational studies report the proportion to be approximately 25% to 53% when restricted to moderate to severe or ‘clinically significant’ pruritus [Hegade, 2019; Mayo, 2023; Veer, 2023, Gungabissoon 2024].

Table 2 Real-world studies reporting the prevalence of pruritus among patients with PBC.

Author (year)	Study Population / Setting	N	Prevalence of Pruritus[1]	Categorization of Pruritus	Pruritus PRO
Gungabissoon (2024)	Patients with PBC in the USA enrolled in the PicnicHealth cohort	225	88.9%	Any patient-reported pruritus (score ≥1)	PBC-40
			53.3%	Clinically significant pruritus (score ≥7)	
Hegade (2019)	UK PBC cohort	2,194	54.8%	Any pruritus (score ≥1)	PBC-40[2]
			26.3%	Mild pruritus (score 4 to 8)	
			16.8%	Moderate pruritus (score 9 to 11)	
			11.7%	Severe pruritus (score ≥12)	
Veer (2023)	Dutch Liver Patients Association members with PBC, as well as patients at outpatient clinic for Erasmus University Medical Center Rotterdam	178	73%	Any pruritus (Current)	Dutch PBC-40
			48%	Mild pruritus (score 1 to 5)	
			21%	Moderate pruritus (score 5 to 10)	
			4%	Severe pruritus (score 11 to 15)	
Mayo (2023)	TARGET-PBC including PBC patients enrolled from 38 academic and community sites across the USA	211	80.6%	Any current pruritus (score ≥1)	PBC-40
			29.9%	Clinically significant pruritus (score ≥7)	

[1]Prevalence of pruritus was estimated as $\frac{number\ of\ PBC\ patients\ wtih\ pruritus\ [variously\ defined]}{total\ number\ of\ PBC\ patients}$

[2]Hegade et al (2019) modified PBC itch domain recall period from "in the last 4 weeks" to "since you developed PBC…"; The PBC-40 itch domain was strongly correlated with ever pruritus NRS (r=0.81, p<0.0001).

SI.1.1 Demographics of the population in the proposed indication and risk factors for the disease

PBC overall is more common among females [Lv, 2021] with a recent study suggesting a female: male ratio or 4 to 6 :1 [Trivella, 2023]. Diagnosis of PBC is typically made between 55 and 65 years; however, patients can present from their 20s onward [Jones, 2018]. Few studies describe prevalence of overall PBC by race/ethnicity; however, a US electronic health records-based study reported 64% of patients with PBC were white; 8% were Black or African American; 7% were Asian American, American Indian, or Pacific Islander; and 21% had unknown race [Lu, 2018].

Few studies have characterized demographic differences and risk factors for pruritus among patients with PBC. However, pruritus can arise at any stage of PBC regardless of biochemical or histological severity, severity of cholestasis, duration of disease, or medical interventions [Hegade, 2016; Düll, 2022]. Across real-world studies of patients with PBC and pruritus, those experiencing clinically significant or severe pruritus tended to be younger and diagnosed at an earlier age [Mayo, 2023; Carbone, 2013; Hegade, 2019]. These patients also frequently exhibit more severe liver disease, characterized by higher alkaline phosphatase (ALP) and total bilirubin levels and a greater prevalence of cirrhosis (including decompensated cirrhosis).

SI.1.2 The main existing treatment options

Currently, approved treatments for PBC include ursodeoxycholic acid (UDCA) for first line treatment. UDCA does not improve itch [Lindor, 2019]. The PPAR agonists, elafibranor (conditionally approved by the EMA in September 2024) and seladelpar (conditionally approved by the EMA in February 2025) are both indicated for adults with an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA. In the clinical trials with PPAR agonists, treatments with elafibranor and seladelpar were associated with an improvement in pruritus compared to placebo as key secondary endpoints [Iqirvo EU SmPC; Lyvdelzi EU SmPC].

For the symptom of cholestatic pruritus, treatment options are limited. Cholestyramine is approved for pruritus associated with partial biliary obstruction and PBC in some regions. Nalfurafine is approved for pruritus in chronic liver disease in Japan. Finally, many other agents and therapies are used off-label with limited evidence (colesevelam, rifampicin, opioid antagonists, sertraline, antihistamines, phototherapy), and for intractable cases, more invasive options like molecular absorbance recirculating system (MARS), nasobiliary drainage, or in rare cases, liver transplant in the absence of liver failure are considered.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

PBC is a progressive liver disease characterized by destruction of small intrahepatic bile ducts, if left untreated, leading to chronic and progressive cholestasis, eventual cirrhosis and liver failure, and complications including portal hypertension, varices, hepatic decompensation, hepatocellular carcinoma, and osteoporosis leading to fractures, [Hirshfield, 2017; Lindor, 2019].

Poor quality of life (QoL) and impaired health status are common in PBC patients [Mells, 2013]. Patients with clinically significant pruritus fare worse than those with mild or no pruritus on all the QoL domains of the PBC-disease specific QoL instrument, PBC-40 (fatigue, social, emotional, cognitive, and other symptoms) [Mayo, 2023]. With PBC, severe treatment-resistant pruritus may also merit consideration for liver transplantation even in the absence of liver failure [Carbone, 2011; EASL, 2017]. Longitudinal studies show that moderate-to-severe pruritus persists for years despite use of on and off-label treatments [Hegade, 2019] and many patients are frequently undertreated, leaving many patients with significant ongoing itch [Mayo, 2023].

SI.1.4 Important co-morbidities

Table 3 summarizes important and prevalent comorbidities among patients with PBC from selected real-world studies; details about non-PBC comparator patients are provided when reported in the included studies. This ensures a comprehensive understanding of the condition with a more accurate evaluation of adverse events in the patient population. Certain comorbidities, such as Sjogren syndrome, autoimmune hepatitis, and cholelithiasis, are more prevalent in PBC patients than in the general population. These conditions could potentially lead to adverse events that may overlap with treatment-emergent adverse events observed in studies.

Table 3 Prevalence of comorbidities among patients with PBC and non-PBC comparator patients from selected real-world studies.[1]

Comorbidity	% of PBC patients[2]	% of non-PBC comparator patients[2,3]	References
Autoimmune diseases			
Autoimmune thyroid disease	1.9 to 13%	0 to 1%	Corpechot (2010), Gershwin (2005), Gungabissoon (2022), Marschall (2019)
Autoimmune hepatitis	2.8 to 9.5%	0 to 0.03%	Bonder (2011), Corpechot (2010), Gungabissoon (2022)
Diabetes Mellitus Type 1	4 to 6.7%	2.5 to 4%	Corpechot (2010), Marschall (2019)
Raynaud syndrome	2.9 to 9%	0.2 to 1%	Corpechot (2010), Gershwin (2005), Gungabissoon (2022)
Rheumatoid arthritis	3 to 10%	1 to 8%	Corpechot (2010), Gershwin (2005), Gungabissoon (2022)
Scleroderma	1 to 2%	0%	Corpechot (2010), Gershwin (2005)
Sjogren syndrome	5.8 to 10%	0 to 0.5%	Corpechot (2010), Gershwin (2005), Gungabissoon (2022)
Systemic Lupus Erythematosus	1 to 3%	0 to 0.5%	Corpechot (2010), Gershwin (2005), Gungabissoon (2022), Marschall (2019)
Non-autoimmune diseases			
Cancer (Overall)	5.3%	5.4%	Marschall (2019)
Cholelithiasis	9.4%	2.9%	Marschall (2019)
Cholecystitis	2.9%	1.1%	Marschall (2019)
Depression	12%	8%	Corpechot (2010)
Diabetes Mellitus Type 2	2 to 4.6%	2.5 to 4%	Corpechot (2010), Marschall (2019)
Fractures	20.8%	NA	Guanabens (2010)
Hypercholesterolemia	58%	46%	Gershwin (2005)
Hypertension	12%	18%	Corpechot (2010), Marschall (2019)
Osteoarthritis	19%	26%	Corpechot (2010)
Osteoporosis	26 to 32.4%	12%	Corpechot (2010), Guanabens (2005)
Urinary tract infection	13.8 to 59%	6.6 to 52%	Corpechot (2010), Gershwin (2005), Gungabissoon (2022)
Abbreviations: NA, not applicable			

Comorbidity	% of PBC patients[2]	% of non-PBC comparator patients[2,3]	References
1 The distribution of comorbidities among patients with PBC and without PBC may differ within and between studies due to true underlying differences; however, these differences in comorbidities (within and between studies) should be interpreted cautiously, as such characteristics can also vary due to a number of factors including study design (e.g., cross-sectional vs. case-control studies); sample selection; how and when the comorbidity was measured; and study country, setting, and time period.			
2 Percentages are reported out to the significant digit reported in each study			
3 Percentages from a referent group are included if included in the underlying study			

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

A range of non-clinical studies have been conducted to support the oral administration of linerixibat in humans. The in vivo non-clinical development program was conducted using mice, rats, rabbits, dogs, and monkeys. These species (except monkey) were chosen since they provided some systemic exposure to linerixibat following oral administration on toxicology studies and the biotransformation of linerixibat in vitro was qualitatively similar between the non-clinical safety species (rats, mice, rabbits, dogs) and humans, demonstrating the relevance of these species for non-clinical safety evaluation.

The overall pharmacokinetic profile of linerixibat after oral administration at pharmacologically relevant doses is consistent with a molecule that is restricted to the intestinal lumen, with minimal absorption, although much higher toxicological doses result in a degree of systemic drug exposure.

A summary of the key safety findings from non-clinical studies and their relevance to human use is presented in Table 4.

KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE:

Table 4 Key Safety findings (from non-clinical studies)

Study type	Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and Repeat dose toxicity		
Gastrointestinal Effects	Non-adverse gastrointestinal effects have been observed in both rat and dog in repeat dose toxicity studies. In the rat minimal to slight mucosal basophilia/hypertrophy with or without inflammatory cell infiltrate was observed in the large intestine with doses ≥1 mg/kg/day in a 14-day study, ≥10 mg/kg/day in the 13-week study, ≥200 mg/kg/day in the 26-week study and ≥250 mg/kg/day in the 2-year carcinogenicity study. The rat intestinal findings were partially reversible following 19-day or 4-week off-dose periods and completely reversible following a 6-week off-dose period in the 26-week study and have not shown progression in severity when linerixibat is given to rats for 2 years. In the dog 14-day study, focal, minimal to mild hemorrhage was observed in the mucosa of the colon and/or rectum of males given ≥100 mg/kg/day and females given 20 or 1000 mg/kg/day. In the dog 13- and 39-week studies, there were no microscopic changes at doses up to 500 mg/kg/day. In addition, dose-related abnormal feces (soft, loose/watery, mucoid, and/or red) were observed after single and repeated oral doses in both rat and dog. The intestinal effects are consistent with GI irritation and may be related to the physicochemical properties of linerixibat itself or due to changes in bile acid flux through the GI tract, a known effect of ileal bile acid transporter inhibitors [Al-Dury, 2018].	The GI effects diarrhea, and abdominal pain have been identified as adverse drug reactions (ADRs) for linerixibat (see Section Part II: Module SVII). There was no evidence of mucosal hemorrhage of the colon and/or rectum related to administration of linerixibat in the clinical development program.
Adrenal effects	Reversible and non-neoplastic, minimal to mild hypertrophy of the adrenal gland zona glomerulosa was observed in rats on the 26- and 104-week studies at doses ≥200 mg/kg/day; not observed in dogs on studies up to 39-weeks at comparable exposures.	There were no findings or events relating to adrenal effects in the linerixibat clinical development program.

Study type	Key Safety findings (from non-clinical studies)	Relevance to human usage
Reproductive Toxicity	Linerixibat did not cause developmental toxicity in embryofetal development studies in rats and rabbits, and had no effect on male and female fertility and early embryonic development in rats. In a pre- and post-natal development study in rats, linerixibat at 50, 200, and 1000 mg/kg/day was administered orally by gavage to F0 female rats from GD 6 through LD 20. There were no linerixibat related effects on the F0 gestation length, parturition, or lactation or on F1 pup survival, early growth, and development. During the postnatal period, there was no linerixibat-related effect on F1 sexual maturation, neurobehavioral function, mating or fertility, parturition, or lactation, or on the survival of F2 generation offspring at any dose. Linerixibat was present in the plasma of offspring (up to 15.3 ng/mL) from dams that received high doses of linerixibat (indicating lactational exposure via milk) without any adverse effects on offspring.	No fertility data are available in humans. There are no or limited amount of data from the use of linerixibat in pregnant women. Systemic absorption following oral administration of linerixibat in humans is minimal, therefore fetal exposure to the drug is also expected to be minimal. As a precautionary measure, it is preferable to avoid the use of Lynavoy during pregnancy. It is unknown whether linerixibat is excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Lynavoy therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother. Relevant information regarding use in pregnancy and lactation is included in the linerixibat labelling.
Genotoxicity/ Carcinogenicity	Linerixibat did not cause gene mutation or chromosomal damage in a bacterial mutagen assay, a chromosomal aberration assay or an in vivo rat bone marrow micronucleus assay. Carcinogenicity studies have been conducted in the rasH2-Tg hemizygous mice for 26 weeks and the Wistar Han rat for at least 104 weeks. In the oral 6-month transgenic RasH2 mouse carcinogenicity study linerixibat was not carcinogenic at	There were no findings from genetic toxicity and carcinogenicity studies that would indicate a significant risk or safety concern of genotoxicity or carcinogenicity in patients administered linerixibat. No signals or safety concerns have been observed or identified in the linerixibat clinical development program (CDP).

Study type	Key Safety findings (from non-clinical studies)	Relevance to human usage
	doses up to 160 mg/kg/day (maximum tolerated dose in the study). When linerixibat was given by oral gavage to Wistar Han rats for 104 weeks at doses of 0 (vehicle), 250, 500, and 1000 mg/kg/day there were no neoplastic findings attributed to linerixibat.	
Safety pharmacology		
Cardiovascular effects	In rats, a single oral linerixibat dose of 1000 mg/kg caused a mild hemodynamic effect (increased heart rate and arterial blood pressure), increased cardiac workload (increased rate pressure-product) and a decrease in PR interval; no effects were observed at doses ≤100 mg/kg. Similar effects were not seen following a 1 hour IV infusion of 10 mg/kg in rats. Steady state plasma linerixibat concentrations were ~3-fold the mean Cmax for highest oral dose. In dogs, oral administration of linerixibat at 1000 mg/kg produced a mild increase in mean arterial pressure (MAP) (~10%) at a single time point of 2 hours post dose. No other changes were observed at this dose or at doses of 20 or 100 mg/kg. There were no treatment-related effects on electrocardiogram (ECG) tracings in dogs at linerixibat doses up to 500 mg/kg/day for 39 weeks.	There were no cardiovascular findings from the safety pharmacology studies that would indicate a significant risk or safety concern in patients receiving linerixibat. No signals or safety concerns have been observed or identified in the linerixibat clinical development program.

Study type	Key Safety findings (from non-clinical studies)	Relevance to human usage
Respiratory effects	In rats, a single oral dose of linerixibat at 2000 mg/kg caused a mild, reversible decrease in total pulmonary ventilation (22.6 to 28.8%) and an increase in total pulmonary resistance (33.3 to 54.5%) from ~1 to 4 hours after dosing. No effects were observed at doses ≤500 mg/kg. Following IV infusion to rats which achieved a steady state plasma concentration 4-fold the mean Cmax observed with a 2000 mg/kg oral dose, there was an increase in total pulmonary ventilation (up to 58%) caused by an increase in tidal volume (up to 39%) there was no effect on pulmonary resistance.	There were no respiratory findings from safety pharmacology studies that would indicate a significant risk for oral administration of linerixibat to humans. No signals or safety concerns have been observed or identified in the linerixibat clinical development program.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Eight Phase 1 studies investigated the PK and PD of linerixibat in healthy volunteers and participants with hepatic impairment (Table 5).

Table 5 Phase 1 Clinical Studies

Study Type	Study Number	Single/Repeat dose	N[a]
FTIH	BAT114985	Single	17
Repeat dose	BSC116511	Repeat	56
Japan single dose	205808	Single	16
Mass balance ADME	205895	Single	6
OCA DDI 90 mg BID	206224	Repeat	19
OCA DDI 40 mg BID	213688	Repeat	52
Food effect	214656	Single	23
Hepatic impairment	214899	Single	16

Source: m5.3.3.1, BAT114985 CSR; m5.3.3.1, BSC116511 CSR; m5.3.3.3, 205808 CSR; m5.3.3.1, 205895 CSR; m5.3.3.4, 206224 CSR; m5.3.3.4, 213688 CSR; m5.3.1.1, 214656 CSR; m5.3.3.3, 214899 CSR.

[a] N=number of participants randomized, except for Study 214899 where N=number of participants enrolled.

Two Phase 2 studies were conducted in PBC patients with cholestatic pruritus. The Phase 2a Study BAT117213 evaluated a linerixibat dose of 45 mg BID increasing to 90 mg BID in a 2-period, 2-week crossover design of linerixibat vs. placebo. The Phase 2b study GLIMMER 201000 was a parallel group design comparing 5 linerixibat dose groups (QD doses of 20 mg, 90 mg, or 180 mg, or BID doses of 40 mg or 90 mg) with placebo over 12 weeks treatment.

One Phase 3 study was conducted (GLISTEN 212620) and one is currently ongoing (LLSAT 212358). GLISTEN 212620 was a parallel group study of 40 mg BID linerixibat versus placebo. It was comprised of 2 parts: Part A, of 24 weeks duration, and Part B, of 8 weeks duration, in which participants from Part A either continued their originally assigned treatment or crossed over to the treatment they were not assigned in Part A. LLSAT 212358 is an open label, uncontrolled, long-term extension study with an initial linerixibat dose of 90 mg BID which was switched to 40 mg BID when that dose was selected for Phase 3.

Table 6 Phase 2 & 3 Clinical Studies in Cholestatic Pruritus in PBC

Study	Phase	Control	Blinding	N[a]	Treatment duration (weeks)
BAT117213	2a	placebo	double blind	22	2[b]
GLIMMER 201000	2b	placebo	double blind	147	12
GLISTEN 212620	3	placebo	double blind	238	24[c]
LLSAT 212358	3	none	open label	215	52[d]

Source: m5.3.4.2, BAT117213 CSR; m5.3.5.1, GLIMMER 201000 CSR; m5.3.5.1, GLISTEN 212620 CSR; m5.3.5.2, LLSAT 212358 CSR.

a. N=number randomized (for non-randomized study LLSAT, N=number of participants who received study treatment).

b. Participants randomized in a crossover fashion to receive placebo or linerixibat in 2 consecutive 2-week periods.

c. Part A of study was of 24 weeks duration, Part B a further 8 weeks.

d. Median weeks of time on linerixibat 40 mg BID.

Linerixibat has been studied in 596 participants (Table 7). A total of 337 participants with PBC (planned trial exposure>1 month) received linerixibat for a duration of 365.71 PY. The safety profile is primarily established from the GLIMMER 201000 (Phase 2b), GLISTEN 212620 (Phase 3) and LLSAT 212358 (Phase 3 Open Label) studies, where study participants with cholestatic pruritus in PBC were treated with linerixibat for a planned duration>1 month; exposure data from these studies are presented in Table 8.

Table 7 Duration of exposure for all studies

Cumulative for all studies	
Duration of exposure to linerixibat (months)	**Number of Participants**
<1	285
1 to <3	82
3 to <6	51
6 to <12	52
≥12	126
≥ 24	60
≥ 36	36
Total	596

Source: LINERIXIBAT GLOBAL ISS Table 1.7

Note: All Safety includes all randomized participants (where applicable) across all studies who have taken at least one dose of linerixibat. Studies included in the analysis are BSC116511, 205895, 214656, 214899, 201351, GLIMMER 201000, LLSAT 212358,

205808, 206224, 213688, BAT114985, 200185, GLISTEN 212620, BAT117213. The total is the unique number of subjects exposed to linerixibat.

Table 8 Duration of exposure (Studies with > 1 Month of Planned Exposure) for Cholestatic pruritus in PBC indication

Cholestatic pruritus in PBC		
Duration of exposure to linerixibat (months)	**Number of Participants**	**Person time (Years)**
<1	26	1.42
1 to <3	82	16.92
3 to <6	51	20.22
6 to <12	52	38.75
≥12	126	288.39
≥ 24	60	193.67
≥ 36	36	136.23
Total person time for indication	337	365.71

Source: LINERIXIBAT GLOBAL ISS Table 1.8

Note: PBC Safety includes all randomized participants across all PBC indication studies who have taken at least one dose of linerixibat. Participants from PBC studies that have more than 1 month of planned exposure of linerixibat (i.e., Study GLISTEN 212620, GLIMMER 201000, LLSAT 212358) are included in this analysis of duration of exposure to linerixibat. The total is the unique number of subjects exposed to linerixibat.

Table 9 Duration of Exposure (Studies with > 1 Month of Planned Exposure) for Cholestatic Pruritus in PBC Indication by Age Group and Sex

	Number of Participants		Person time (Years)	
Age group (years)	**Male**	**Female**	**Male**	**Female**
<45	4	47	1.24	47.67
45 to 54	1	107	0.08	122.74
55 to 64	2	92	1.68	98.56
65 to 74	10	61	12.50	69.01
≥75	3	10	0.44	11.79
<65	7	246	3.00	268.97
≥65	13	71	12.94	80.80
Total	20	317	15.94	349.77

Source: LINERIXIBAT GLOBAL ISS Table 1.9

Note: PBC Safety includes all randomized participants across all PBC indication studies who have taken at least one dose of linerixibat. Participants from PBC studies that have more than 1 month of planned exposure of linerixibat (i.e., Study GLISTEN 212620, GLIMMER 201000, LLSAT 212358) are included in this analysis of duration of exposure to linerixibat. The total is the unique number of subjects exposed to linerixibat irrespective of age category.

Table 10 Duration of Exposure (Studies with > 1 Month of Planned Exposure) for Cholestatic Pruritus in PBC Indication by Specific Dose Group

Dose group	Number of Participants	Person time (Years)
Linerixibat 20 mg QD	16	3.70
Linerixibat 90 mg QD	23	5.02
Linerixibat 180 mg QD	27	4.98
Linerixibat 40 mg BID	277	309.69
Linerixibat 90 mg BID	66	37.50
Total	337	365.71

Source: LINERIXIBAT GLOBAL ISS Table 1.11

Note: PBC Safety includes all randomized participants across all PBC indication studies who have taken at least one dose of linerixibat. Participants from PBC studies that have more than 1 month of planned exposure of linerixibat (i.e., Study GLISTEN 212620, GLIMMER 201000, LLSAT 212358) are included in this analysis of duration of exposure to linerixibat. Subjects may appear in multiple dose groups as they are counted in each dose they were exposed to. The total number of subjects is the number of subjects exposed to any one linerixibat dose and are only counted once.

Table 11 Duration of Exposure (Studies with > 1 Month of Planned Exposure) for Cholestatic Pruritus in PBC Indication by Race

Race	Number of Participants	Person time (Years)
American Indian or Alaska Native	7	9.05
Asian - Central/South Asian Heritage	0	0
Asian - East Asian Heritage	31	16.21
Asian - Japanese Heritage	69	126.40
Asian - South East Asian Heritage	0	0
Black or African American	2	3.18
Native Hawaiian or Other Pacific Islander	0	0
White - White/Caucasian/European Heritage	205	194.95
White - Arabic/North African Heritage	6	2.70
Mixed Asian	0	0

Race	Number of Participants	Person time (Years)
Mixed White	0	0
Mixed	3	0.52
Not Captured	14	12.71
Total	337	365.71

Source: LINERIXIBAT GLOBAL ISS Table 1.10

Note: PBC Safety includes all randomized participants across all PBC indication studies who have taken at least one dose of linerixibat. Participants from PBC studies that have more than 1 month of planned exposure of linerixibat (i.e., Study GLISTEN 212620, GLIMMER 201000, LLSAT 212358) are included in this analysis of duration of exposure to linerixibat.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Linerixibat has not been studied in pregnant or lactating women, patients with severe renal impairment or severe hepatic impairment (HI).

There is no missing information that is relevant for the approved indication.

The exposure by race is presented in Table 11 (Duration of Exposure (Studies with > 1 Month of Planned Exposure) for Cholestatic Pruritus in PBC Indication by Race). It is not expected that race will lead to meaningful differences in the safety profile.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 12 Exclusion criteria

Criterion	Reason for exclusion	Is it considered missing information? (YES/NO)	Rationale
Current significant diarrhea	To minimize the risk to participants and to reduce interference with the assessment of the identified risk of diarrhea.	No	Diarrhea is an Identified Risk for linerixibat. It is not considered to meet the criteria of an Important Risk (see PART II: Module SVII).
Active inflammatory ileal disease	To minimize the risk to participants and to reduce interference with the assessment of linerixibat safety and efficacy. Linerixibat acts in the distal ileum of the GI tract.	No	It is not anticipated that linerixibat would pose a risk to participants with active inflammatory ileal disease; however, they may benefit from the treatment.

Criterion	Reason for exclusion	Is it considered missing information? (YES/NO)	Rationale
Current symptomatic cholelithiasis or inflammatory gallbladder disease (cholecystitis).	To minimize the risk to participants and to reduce interference with the assessment of the potential risk of cholecystitis or symptomatic gallstones (cholelithiasis). It is unknown whether linerixibat increases the risk of symptomatic gallstones or cholecystitis by its mechanism of action (due to interruption of enterohepatic recirculation of BA). Genetic studies suggest that variants in the *SLC10A2* gene leading to either a reduction or lack of function (LOF) in IBAT are associated with an increased risk of gallbladder disease.	No	Cholecystitis or symptomatic gallstones (cholelithiasis) is considered as a Potential Risk. It is not considered to meet the criteria of an Important Risk (see PART II: Module SVII).

Criterion	Reason for exclusion	Is it considered missing information? (YES/NO)	Rationale
Any current malignancies (including hematologic and solid malignancies).	To minimize the risk to participants and to reduce interference with the assessment of linerixibat safety profile.	No	Non-clinical assessments suggest that linerixibat does not pose a genotoxic or carcinogenic hazard to humans. It is not anticipated that the safety profile will differ in patients with current malignancy.
History of bariatric surgery with ileal bypass at any time.	Linerixibat acts in the distal ileum of the GI tract. Therefore, there is a potential that bariatric surgery with ileal bypass will reduce the efficacy of linerixibat.	No	It is not expected that linerixibat will be used in participants with ileal bypass.
History of any bariatric surgery performed in the past 3 years.	To minimize the potential risk to participants during characterization of the safety profile, and to minimize cofounding with the assessment of linerixibat safety profile.	No	There is no evidence to suggest that linerixibat would pose a risk to participants with a history of other bariatric surgery.
Screening ALT > 6x ULN in a single baseline measure or ALT > 5x ULN using the average of two baseline measures. Total bilirubin >2.0 x ULN using the average of two baseline measures.	To minimize the risk to participants and to reduce interference with the assessment of linerixibat safety profile.	No	Liver laboratory parameters are routinely monitored in PBC patients as part of standard care. More frequent monitoring may be required if elevations are observed.

Criterion	Reason for exclusion	Is it considered missing information? (YES/NO)	Rationale
Hepatic decompensation (e.g., variceal bleeding, hepatic encephalopathy or ascites).	As patients are at risk of further deterioration of their existing disease, and to minimize cofounding with the assessment of linerixibat safety profile, these participants were excluded.	No	Clinical guidelines recommend these patients should be treated for their hepatic decompensation, rather than their symptoms. [Regev, 2019]. It is not anticipated that linerixibat will be used in this population.
Severe renal impairment (defined as estimated glomerular filtration rate (eGFR <30ml/min/1.73m^2).	To minimize the risk to participants and to reduce interference with the assessment of linerixibat safety profile.	No	Renal elimination is a minor clearance pathway for linerixibat. Thus, renal impairment would not significantly increase systemic exposure to linerixibat. Therefore, it is not anticipated the safety profile will differ in patients with severe renal impairment.
Pregnancy and Lactation	The safe use of linerixibat during human pregnancy and breastfeeding has not been established.	No	There was no evidence of embryofetal harm or adverse pregnancy outcomes in animal studies at clinically relevant exposures (see Part II: Module SII). Guidance for the prescriber and patient will be included in the linerixibat labelling.

Criterion	Reason for exclusion	Is it considered missing information? (YES/NO)	Rationale
Patients under 18 years of age.	Information required for initial marketing authorization was for adults only.	No	Linerixibat is intended for use in adults only, therefore it is not anticipated to be used in this population.
Use of obeticholic acid: within 8 weeks prior to screening.	Based on results from two drug-drug interaction studies a pharmacokinetic (PK) drug-drug interaction (DDI) was confirmed with obeticholic acid. OCA has a W&P on the label for causing itch, therefore it was excluded from clinical trials to reduce interference with the assessment of linerixibat efficacy.	No	It is not anticipated the safety profile of linerixibat will differ in participants receiving OCA. However, this interaction may decrease the efficacy of OCA. It is recommended to monitor the biochemical response (e.g., ALP and bilirubin) during treatment with OCA when patients initiate linerixibat.
Infection with human immunodeficiency virus (HIV).	This is a standard exclusion criterion due to the consideration that this medical condition could confound safety results with linerixibat.	No	It is not anticipated that the safety profile of linerixibat will differ in patients with HIV.
Patients with primary sclerosing cholangitis (PSC), alcoholic liver disease, hepatitis B or C (HBV, HCV) infection.	These chronic liver diseases could impact assessment of safety and efficacy in the intended population (PBC) and may impact liver function tests, affecting safety assessment with linerixibat.	No	It is not anticipated that the safety profile of linerixibat will differ in these patients.
Confirmed hepatocellular carcinoma or biliary cancer.	These medical conditions could impact assessment of safety and efficacy of linerixibat.	No	It is not anticipated that the safety profile of linerixibat will differ in these patients.

QTc >480 msec	Standard exclusion criteria to minimize the risk of including participants with a predisposition to arrhythmias and confounding the safety analysis.	No	There is no evidence (from pre-clinical and clinical studies) that linerixibat increases QTc interval or risk of arrhythmias. It is not anticipated that the safety profile will differ in these patients.

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program is unlikely to detect certain types of adverse reactions such as uncommon, rare, very rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, as the total linerixibat exposure was 596 participants.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Table 13 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the CDP. Woman of Childbearing Potential (WOCBP) were allowed to participate in clinical trials of linerixibat upon an agreement to follow contraception requirements and the provision of written informed consent. There were no pregnancies reported in linerixibat CDP.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	

Patients with hepatic impairment	Hepatic impairment Linerixibat has been studied in PBC patients with compensated cirrhosis (i.e. absence of history or presence of hepatic decompensation and total bilirubin <2 x ULN). In the pooled safety dataset, 23 participants in the linerixibat 40 mg BID treatment group had cirrhosis at baseline. In the LLSAT study, 17 participants had hepatic cirrhosis recorded as a baseline medical condition received linerixibat (this may include participants included in the pooled safety dataset). In the HI study, 8 participants with moderate hepatic impairment (Child- Pugh B) received a single 40 mg dose of linerixibat. Patients with severe hepatic impairment (Child-Pugh C) were excluded from the linerixibat CDP.
Patients with renal impairment	**Renal impairment** Participants with mild and moderate renal impairment (defined as GFR ≥ 30 and < 90 ml/min/1.73m²) were allowed to participate in the phase 3 clinical trials of linerixibat. In the GLISTEN study, 68 participants with mild renal impairment (defined as eGFR 60 to <90 ml/min/1.73m2) and 10 participants with moderate renal impairment (defined as eGFR 30 to <60 ml/min/1.73m2) at baseline were exposed to linerixibat. Additionally, 1 participant had eGFR < 30 mL/min/1.73m2 prior to starting study intervention. In the LLSAT study, 112 participants with mild renal impairment (defined as eGFR 60 to <90 ml/min/1.73m2) and 15 participants with moderate renal impairment (defined as eGFR 30 to <60 ml/min/1.73m2) at baseline were exposed to linerixibat (this may include participants included in the pooled safety dataset).
Patients with cardiovascular impairment	There were no cardiovascular exclusion criteria in the linerixibat clinical trial program, reflecting the patient population.
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	No ethnicities were excluded from the clinical development program. See Table 11 (Duration of Exposure (Studies with > 1 Month of Planned Exposure)) for Cholestatic Pruritus in PBC Indication by Race).

Subpopulations carrying relevant genetic polymorphisms	Genetic studies suggest that variants in the SLC10A2 gene leading to either a reduction or LOF in IBAT are associated with an increased risk of gallbladder disease. 20 GLISTEN participants consented to genetic testing and had genotypes from 5 SLC10A2 genetic variants impacting IBAT function measured from saliva-extracted DNA. 3 of the 20 GLISTEN participants were heterozygous carriers (carried one minor allele) for one of the two SLC10A2 genetic variants that reduce function of the IBAT and also were genotyped (rs55971546 and rs60380298). 2 of these 3 heterozygous carriers were exposed to linerixibat.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-authorization exposure

There is no data for this section as linerixibat has not been marketed in any country.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Considering the mechanism of action, linerixibat is not anticipated to show a potential for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

The following risks are considered not important for inclusion in the list of safety concerns in the RMP:

- Gastrointestinal disorders including diarrhea and abdominal pain
- Cholecystitis or symptomatic gallstones (cholelithiasis)

REASON FOR NOT INCLUDING AN IDENTIFIED OR POTENTIAL RISK IN THE LIST OF SAFETY CONCERNS IN THE RMP:

Known risks that do not impact the risk-benefit profile:

Gastrointestinal disorders including diarrhea and abdominal pain

Diarrhea and abdominal pain were reported more commonly in participants receiving linerixibat than placebo. In most cases, adverse events (AEs) of diarrhea were mild in intensity. The majority of participants who experienced AEs of diarrhea were able to continue study treatment without treatment discontinuation or interruption and recovered from the event. If necessary, symptoms could be managed with antidiarrheals. These findings were consistent with the interim data of the ongoing long-term safety study. There were no reports of serious GI events being related to treatment with linerixibat or consequent to AEs of diarrhea, or abdominal pain. Gastrointestinal events (diarrhea, and abdominal pain) are included in the ADRs section of the linerixibat labelling.

Based on the available data from the CDP with linerixibat it is considered that the observed GI effects have minimal clinical impact on patients in relation to the severity of the indications treated. These events can be followed up via routine pharmacovigilance (PV) with no requirement for additional characterization, and no additional risk minimization measures are necessary. Thus, GI effects, are not considered to meet the criteria of an important risk.

Cholecystitis or symptomatic gallstones (cholelithiasis)

Genetic studies suggest that variants in the *SLC10A2* gene leading to either a reduction or LOF in IBAT are associated with an increased risk of gallbladder disease (224293 Study Report).

In the pooled safety dataset, the number of participants who experienced events of cholecystitis and symptomatic cholelithiasis was similar between treatment groups during blinded treatment. The majority of events of cholecystitis or symptomatic gallstones observed in the CDP program were serious due to hospitalization, none were severe in intensity. Most events were not considered to be related to study treatment by the investigator and all participants continued to receive linerixibat. There was no pattern in time to onset. Due to the nature of PBC all participants are at increased risk of events of cholecystitis. The overall incidence of cholecystitis or symptomatic gallstones within the PBC CDP is consistent with the background rate of cholecystitis and/or cholelithiasis in the PBC population (18.96 to 37.91 per 1000 PY) (220783 CSR, Section 7).

Whilst the clinical data are not suggestive of an increased likelihood of events of cholecystitis and symptomatic cholelithiasis in participants receiving linerixibat, it is recognized that the CDP would be unlikely to have sufficient power to quantify the risk of a low frequency event such as cholecystitis and symptomatic cholelithiasis. Therefore, due to the genetic study data, cholecystitis and symptomatic cholelithiasis are to be considered a potential risk for linerixibat treatment.

Based on the available data from the CDP, cholecystitis or symptomatic cholelithiasis is not considered to impact the benefit risk for participants treated with linerixibat. These events can be followed up via routine pharmacovigilance with no requirement for additional PV activities to characterize the risk, and no additional risk minimization measures are necessary. Thus, cholecystitis or symptomatic cholelithiasis, is not considered to meet the criteria of an important risk.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: None

Important Potential Risk: Hepatotoxicity

Risk-Benefit Impact:

Hepatotoxicity has been classified as an important potential risk due to its potential clinical significance and potential impact on the benefit-risk balance. In the linerixibat CDP, transaminase (ALT and AST) increases occurred more commonly in participants receiving linerixibat than placebo. Further investigation is needed to determine whether linerixibat poses a hepatotoxicity risk.

Missing Information: Safety (e.g., consequences of diarrhea) in elderly and very elderly patients

Risk-Benefit Impact:

In the linerixibat CDP, no specific safety concerns were identified in elderly participants aged ≥65 years; however a higher proportion of serious adverse events (SAEs) in the linerixibat group was noted compared with placebo in the older age groups. Data regarding diarrhea, the most common AE associated with linerixibat, demonstrated higher incidence of diarrhea in elderly participants following linerixibat exposure compared with placebo.

Since limited data exists regarding the safety of linerixibat in the older population, safety (e.g., consequences of diarrhea) in elderly and very elderly patients has been included in the list of safety concerns as the missing information to adequately characterize the safety profile in this population.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

This section is not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risk: None

Important potential risk: Hepatotoxicity

Potential Mechanism	The mechanism for potential hepatocellular toxicity of linerixibat is not known.
Evidence source(s) and strength of evidence	There was no evidence of hepatotoxicity in toxicology studies at maximum tolerated doses in rats and dogs (exposures up to 140- to 145-fold clinical exposure at Ph3 dose of 40 mg BID and 22-fold clinical exposure at a dose of 90 mg BID). Increased levels of ALT and AST have been observed with other IBAT inhibitors. It has been postulated that these ALT increases are a transient asymptomatic effect of IBAT inhibition. Hepatic cholesterol depletion possibly affecting membrane integrity and the initial compensatory increase in bile acid synthesis have been hypothesized as a plausible explanation for this

	effect for both volixibat and cholestryamine [Singhal, 2014; Herzog, 2016; Newsome, 2020]. In clinical trials, treatment emergent transaminase elevations were observed in some participants with PBC as well as healthy participants following linerixibat exposure; most of the transaminase elevations were non-serious and transient. Across GLISTEN and LLSAT pivotal clinical trials, 16 participants receiving linerixibat had liver laboratory biochemistry meeting the protocol-defined liver stopping criteria of which 5 were adjudicated by the Hepatic Safety Panel (HSP) as possibly related to linerixibat. The adjudication of "possibly related" was based on the absence of clear alternative etiologies rather than direct evidence implicating linerixibat. There was no laboratory evidence indicating that linerixibat causes drug induced liver injury. Due to the limited clinical evidence of hepatic injury associated with linerixibat, further evaluation is needed.
Characterization of the risk	In the pooled safety dataset (GLIMMER and GLISTEN Part A), AEs within the Liver Related Adverse Events Standardised MedDRA Query (SMQ) were more frequently reported in the linerixibat group compared with placebo, primarily increases in ALT and AST. Adverse Events within the MedDRA SMQ 'Drug-related hepatic disorders' were reported in 22 (15%) participants in the linerixibat group vs 10 (8%) on placebo. All AEs in the linerixibat group were mild or moderate and 2 AEs in placebo group were severe. Study treatment was permanently discontinued in 4% of participants in the linerixibat group and 2% of participants in placebo group. In LLSAT clinical trial, a total of 34 (16%) participants experienced AEs within Liver Related Adverse Events SMQ. There was one case of drug-induced liver injury, which was adjudicated as possibly related to linerixibat by the HSP based on the following: firstly, liver function test changes could not be separated temporally (in a convincing manner) from the co-administered medicinal product start/stop and

	linerixibat start/stop and secondly, there were no other alternative causes at the time of the liver event other than a conclusion of possible drug-induced liver injury. Increased liver laboratory parameters (ALT, AST, ALP and TB) meeting the protocol defined liver stopping criteria have been observed in the linerixibat pivotal studies. In GLISTEN Part A, 9 participants had liver elevations that met the protocol defined liver stopping criteria; 7 participants in the linerixibat group and 2 participants in the placebo group. Three of these liver stopping events in the linerixibat group were adjudicated by the HSP as “possible”; and 4 other events were adjudicated as “unlikely/not related” to linerixibat. There were 2 participants in LLSAT trial who experienced liver stopping events that the HSP adjudicated the causality to study treatment as ‘possible’. All liver stopping events adjudicated as ‘possible’ were non-serious. No elevations in liver enzymes meeting liver stopping criteria were adjudicated as "probably" or "definitely" related to linerixibat by the HSP. In the pooled safety dataset, linerixibat was associated with more frequent shifts to above ULN liver tests and greater mean increases in ALT, AST, ALP, and total bilirubin versus placebo. Approximately 5% of participants in the open-label LLSAT experienced concurrent marked transaminase and bilirubin elevations (ALT and/or AST ≥3×ULN with TB ≥2×ULN), with 9 of 11 meeting stopping/monitoring criteria.
Risk factors and risk groups	Currently, there are no risk factors or groups that have been observed to be at risk for potential hepatotoxicity following linerixibat treatment. It can be expected that elevations in liver biochemistry, including transaminases, may vary according to the stage of the underlying disease. In the pooled safety dataset, participants with abnormal liver laboratory parameters at baseline experienced greater occurrence of increases in transaminases during the clinical trial.

	The safety of linerixibat has not been established in patients with severe hepatic impairment (Child-Pugh C).
Preventability	Currently, there are no data on predictability of potential hepatotoxicity or factors that could increase the risk of hepatotoxicity with administration of linerixibat. However, early detection of elevations of liver enzymes could mitigate occurrence of potential liver injury and its severity. It is recommended that baseline ALT and AST levels be obtained prior to initiation of linerixibat treatment and transaminases be monitored during treatment according to routine standard clinical practice for PBC patients. More frequent monitoring may be required for transaminase elevations, and if they persist, the healthcare provider should weigh the potential risks against the benefit of continuing treatment.
Impact on the benefit-risk	Elevations in liver transaminases have been observed in participants exposed to linerixibat. Although some events may be attributable to underlying liver disease or other confounders, a close temporal relationship, a positive de-challenge for some of the received cases support a reasonable possibility of a causal relationship between linerixibat and transaminase elevations. There was no laboratory evidence indicating that linerixibat causes hepatic injury. Nevertheless, further investigation is needed to ascertain whether linerixibat poses a risk of hepatotoxicity. With the currently available efficacy data, the benefit–risk balance of linerixibat is considered favorable for patients with PBC experiencing pruritus.
Public Health Impact	Given the rare nature of the PBC indication and low reporting rate of hepatic events during linerixibat CDP, the public health impact of this potential risk is considered to be low.

SVII.3.2 Presentation of the missing information

Missing information: Safety (e.g., consequences of diarrhea) in elderly and very elderly patients

Evidence Source:	Across the key clinical trials (GLISTEN, LLSAT, GLIMMER), a total of 84 participants aged ≥65 years were exposed to linerixibat and 13 participants aged ≥75 years, representing approximately 25% and 4% of the total study population, respectively. No specific safety concerns were identified in elderly participants aged ≥65 years. Overall, in the pooled safety dataset, the incidence of AEs in the linerixibat group was comparable across the age groups (adults 88%; elderly [≥65 to <75 years] 93%; very elderly [≥75 years] 100%). Nonetheless, the incidence of SAEs in the linerixibat group increased with age (adults 8%; elderly 14%; very elderly 33%). Higher percentage of SAEs in the linerixibat group was noted compared with placebo in the older age groups In LLSAT clinical trial. diarrhea was more commonly reported in participants aged ≥65 years (75% [41/56]) compared with the very elderly participants (50% [4/8)]. Adverse events leading to study withdrawal in the linerixibat group occurred in 3 (3%) adults, 1 (4%) elderly participant and 1 (33%) very elderly participant. In the pooled safety dataset from GLIMMER and GLISTEN Part A, the most frequently reported AE in elderly and very elderly participants was diarrhea. The AE was reported more often in the linerixibat group than in the placebo group: among participants aged ≥65 years, 68% (19/28) in the linerixibat group reported diarrhea compared with 23% (7/30) in the placebo group; among those aged ≥75 years, 67% (2/3) in the linerixibat group reported diarrhea, whereas no cases were reported in the placebo group (0/7). There was no evidence of increased severity or clinical sequalae reported in elderly or very elderly participants compared with overall population. In the CDP, elderly and very elderly population were represented and no specific safety concerns were identified. However, given the low incidence of PBC in general population and the limited population enrolled into clinical trials, limited data exists on the safety of linerixibat in older age groups. Safety (e.g., consequences of diarrhea) in elderly and very elderly patients has been classified as missing information as further evaluation is required.
Population in need of further characterization	Safety profile in elderly and very elderly patients will continue to be evaluated through routine and additional pharmacovigilance activities.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14 Summary of safety concerns Summary of safety concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity
Missing information	Safety (e.g., consequences of diarrhea) in elderly and very elderly patients

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORIZATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection in the pharmacovigilance plan.

III.2 Additional pharmacovigilance activities

Study 212358 LLSAT Summary

212358 LLSAT: "Long-term Safety and Tolerability Study of Linerixibat for the Treatment of Cholestatic Pruritus in Participants with Primary Biliary Cholangitis"

Rationale and Study Objectives:

- **Primary Objective**:

- To evaluate the safety and tolerability of long-term linerixibat treatment in participants with cholestatic pruritus in PBC

- **Secondary Objective**:

- To characterize the effects of long-term linerixibat treatment on disease burden and health-related quality of life (QoL) in participants with cholestatic pruritus in PBC
- To characterize the effects of long-term linerixibat treatment in participants with cholestatic pruritus in PBC

Additional secondary objectives for Group 2 (GLISTEN participants) only:

- To evaluate the maintenance of efficacy of linerixibat on itch over 52 weeks.
- To evaluate the effect of linerixibat on health-related QoL

Study Design:

Open-label, international multi-centre, long-term interventional study

Study Population:

This study population comprises participants who previously participated in the Phase 2 study 201000 (GLIMMER) and in the Phase 3 study 212620 (GLISTEN).

Milestones:

Final Study Report submission: March 2027.

III.3 Summary Table of additional Pharmacovigilance activities

Table 15 On-going and planned additional pharmacovigilance activities

Study *Status*	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Study *Status*	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Study 212358 LLSAT Long-term Safety, Tolerability Study of linerixibat for the Treatment of Cholestatic Pruritus in Participants with Primary Biliary Cholangitis *Ongoing*	**Primary Objective** • To evaluate the safety and tolerability of long-term linerixibat treatment in participants with cholestatic pruritus in PBC **Secondary Objective** • To characterize the effects of long-term linerixibat treatment on disease burden and health-related quality of life (QoL) in participants with cholestatic pruritus in PBC • To characterize the effects of long-term linerixibat treatment in participants with cholestatic pruritus in PBC **Additional secondary objectives for Group 2 (GLISTEN participants) only** • To evaluate the maintenance of efficacy of linerixibat on itch over 52 weeks. • To evaluate the effect of linerixibat on health-related QoL	• Hepatoxicity • Safety (e.g., consequences of diarrhea) in elderly and very elderly patients	Final Study Report submission	March 2027

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There is no post-authorization efficacy study proposed for this product.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 16 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Hepatotoxicity	**Routine risk communication:** • SmPC sections 4.2, 4.4, 4.8 • PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations for obtaining baseline transaminase (ALT and AST) levels prior to initiating treatment with linerixibat and their monitoring during treatment per standard clinical practice are included in SmPC sections 4.4 and PL section 2. • Recommendations for considering more frequent monitoring of ALT and AST levels in case of transaminase elevations are included in SmPC sections 4.4. • Recommendations for weighing the potential risks against the benefit of continuing treatment if transaminase elevations persist are included in SmPC sections 4.4. **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine
Safety (e.g., consequences of diarrhea) in elderly and very elderly patients	**Routine risk communication:** • SmPC section 4.2 • PL none **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimization activities
	• None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimization measures

Table 17 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimization measures: • SmPC section 4.2, 4.4, 4.8 • PL section 2 • SmPC section 4.4 and PL section 2 where advice is given on obtaining transaminase (ALT and AST) levels prior to initiation of linerixibat treatment and their monitoring during treatment according to routine standard clinical practice for PBC patients. • SmPC section 4.4 where recommendations are given for considering more frequent monitoring of ALT and AST levels in case of transaminase elevations. • SmPC section 4.4 where recommendations are given for weighing the potential risks against the benefit of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 212358 LLSAT

Safety concern	Risk minimization measures	Pharmacovigilance activities
	continuing treatment if transaminase elevations persist. • Prescription only medicine Additional risk minimization measures: • None	
Safety (e.g., consequences of diarrhea) in elderly and very elderly patients	Routine risk minimization measures: • SmPC section 4.2 • Prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 212358 LLSAT

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for LYNAVOY (linerixibat)

This is a summary of the risk management plan (RMP) for LYNAVOY. The RMP details important risks of LYNAVOY, how these risks can be minimized, and how more information will be obtained about LYNAVOY's risks and uncertainties (missing information).

LYNAVOY's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LYNAVOY should be used.

This summary of the RMP for LYNAVOY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of LYNAVOY's RMP.

I. The medicine and what it is used for

LYNAVOY is authorized for the treatment of cholestatic pruritus in adult patients with primary biliary cholangitis (PBC).– (see SmPC for the full indication). It contains linerixibat as the active substance and it is administered orally.

Further information about the evaluation of LYNAVOY’s benefits can be found in LYNAVOY’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of LYNAVOY, together with measures to minimize such risks and the proposed studies for learning more about LYNAVOY's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to

ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment -so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of LYNAVOY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of LYNAVOY are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LYNAVOY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Hepatotoxicity
Missing information	Safety (e.g., consequences of diarrhea) in elderly and very elderly patients

II.B Summary of important risks

Important potential risk	**Hepatotoxicity**
Evidence for linking the risk to the medicine	In clinical trials, treatment emergent transaminase elevations were observed in some participants with PBC as well as healthy participants following linerixibat exposure; most of the transaminase elevations were non-serious and transient.

	Across GLISTEN and LLSAT pivotal clinical trials, 16 participants receiving linerixibat had liver laboratory biochemistry meeting the protocol-defined liver stopping criteria of which 5 were adjudicated by the HSP as possibly related to linerixibat. The adjudication of "possibly related" was based on the absence of clear alternative etiologies rather than direct evidence implicating linerixibat. There was no laboratory evidence indicating that linerixibat causes drug induced liver injury. Due to the limited clinical evidence of hepatic injury associated with linerixibat, further evaluation is needed.
Risk factors and risk groups	Currently, there are no risk factors or groups that have been observed to be at risk for potential hepatotoxicity following linerixibat treatment. It can be expected that elevations in liver biochemistry, including transaminases, may vary according to the stage of the underlying disease. In the pooled safety dataset, participants with abnormal liver laboratory parameters at baseline experienced greater occurrence of increases in transaminases during the clinical trial. The safety of linerixibat has not been established in patients with severe hepatic impairment (Child-Pugh C).
Risk minimization measures	<u>Routine risk minimization measures:</u> • SmPC section 4.2, 4.4, 4.8 • PL section 2 • SmPC section 4.4 and PL section 2 where advice is given on obtaining transaminase (ALT and AST) levels prior to initiation of linerixibat treatment and their monitoring during treatment according to routine standard clinical practice for PBC patients.

	• SmPC section 4.4 where recommendations are given for considering more frequent monitoring of ALT and AST levels in case of transaminase elevations. • SmPC section 4.4 where recommendations are given for weighing the potential risks against the benefit of continuing treatment if transaminase elevations persist. • Prescription only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 212358 LLSAT See section II.C of this summary for an overview of the post-authorization development plan.

Missing information	**Safety (e.g., consequences of diarrhea) in elderly and very elderly patients**
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2 • Prescription only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 212358 LLSAT See section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of LYNAVOY.

II.C.2 Other studies in post-authorization development plan

212358 LLSAT: “Long-term Safety and Tolerability Study of Linerixibat for the Treatment of Cholestatic Pruritus in Participants with Primary Biliary Cholangitis”

Primary Objective:

- To evaluate the safety and tolerability of long-term linerixibat treatment in participants with cholestatic pruritus in PBC

Secondary Objective:

- To characterize the effects of long-term linerixibat treatment on disease burden and health-related quality of life (QoL) in participants with cholestatic pruritus in PBC
- To characterize the effects of long-term linerixibat treatment in participants with cholestatic pruritus in PBC

Additional secondary objectives for Group 2 (GLISTEN participants) only:

- To evaluate the maintenance of efficacy of linerixibat on itch over 52 weeks.
- To evaluate the effect of linerixibat on health-related QoL

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.