EU Risk Management Plan for
Lyvdelzi (seladelpar)

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RMP version to be assessed as part of this application:

Version Number	Data Lock Point for This RMP	Date of Final Sign-off
1.1	13 February 2025	Refer to ELECTRONIC SIGNATURES

Rationale for submitting an updated RMP:

Availability of Clinical Study Report for Study CB8025-21838.

Change of the brand name from Seladelpar Gilead to Lyvdelzi.

Update to the format of the RMP.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant Changes to RMP
Part II Safety Specification	Part II: Module SI—Epidemiology of the Indication(s) and Target Populations(s)	None
	Part II: Module SII—Nonclinical Part of the Safety Specification	None
	Part II: Module SIII—Clinical Study Exposure	Updated with data up to 13 February 2025
	Part II: Module SIV—Populations Not Studied in Clinical Studies	None
	Part II: Module SV—Postauthorization Experience	Updated with data up to 13 February 2025
	Part II: Module SVI—Additional EU Requirements for the Safety Specification	None
	Part II: Module SVII—Identified and Potential Risks	Updates made based on completed Study CB8025-21838
	Part II: Module SVIII—Summary of the Safety Concerns	Updated based on data from completed Study CB8025-21838
Part III Pharmacovigilance Plan		Updated based on data from completed Study CB8025-21838

Part	Module/Annex	Significant Changes to RMP
Part IV Plan for Postauthorization Efficacy Studies		None
Part V Risk Minimization Measures		Updated based on data from completed Study CB8025-21838
Part VI Summary of the Risk Management Plan		Updated based on data from completed Study CB8025-21838
Part VII Annexes		Updated based on data from completed Study CB8025-21838

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

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1.0	EMEA/H/C/004692/0000	20 February 2025

QPPV name: Rainer Heissing

QPPV signature: Refer to ELECTRONIC SIGNATURES

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GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	adverse drug reaction
AE	adverse event
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
CoA	acetyl coenzyme A
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum concentration
CP	Child Pugh
CYP	cytochrome P450
EASL	European Association for the Study of the Liver.
EC_{50}	50% effective concentration
ECG	electrocardiogram
EPAR	European Public Assessment Report
eGFR	estimated glomerular filtration rate
EEA	European Economic Area
EFS	event-free survival
EM	electron microscope
EMA	European Medicines Agency
EU	European Union
EU-RMP	EU Risk Management Plan
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FCoA	atty acyl-coenzyme A
GI	gastrointestinal
GLP	good laboratory practice
GWAS	genome-wide association studies
HB	haemoglobin
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCT	haematocrit
HCV	hepatitis C virus
HDL	high density lipoprotein
hERG	human ether-a-go-go-related gene
HI	hepatic impairment

HIV	human immunodeficiency virus
HLA	human leucocyte antigen
IL	interleukin
IM	intermediate metaboliser
INN	International nonproprietary name
IP	intra-peritoneal
LDL	low density lipoprotein
LOAEL	lowest observed adverse event level
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for End-Stage Liver Disease
MOA	mechanism of action
NOAEL	no observed adverse event level
OCA	obeticholic acid
PBC	primary biliary cholangitis
PHT	portal hypertension
PL	package leaflet
PK	pharmacokinetics
PM	poor metaboliser
PPAR	peroxisome proliferator receptor
PSC	primary sclerosing cholangitis
PSUR	periodic safety update report
QoL	quality of life
QTc	corrected QT
RBC	red blood cells
RNA	ribonucleic acid
RR	rate ratio
SAE	serious adverse event
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TNF	tumor necrosis factor
UDCA	ursodeoxycholic acid
UDP	uridine diphosphate
UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
US	United States of America

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Seladelpar
Pharmaco-therapeutic group(s) (ATC code):	A05AX07 (Bile and liver therapy, other drugs for bile therapy)
Marketing authorisation holder	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA):	Lyvdelzi.
Marketing authorization procedure:	Centralized
Brief description of the product:	**Chemical class:** Peroxisome proliferator receptor (PPAR) delta (PPARδ) agonist
	Summary of mode of action: Seladelpar is a potent and selective PPARδ agonist, or delpar. PPARδ is a nuclear receptor expressed in the liver and other tissues. PPARδ activation reduces bile acid synthesis in the liver through fibroblast growth factor 21 (FGF21)-dependent downregulation of CYP7A1, the key enzyme for the synthesis of bile acids from cholesterol and by decreasing cholesterol synthesis and absorption. These actions result in lower bile acid exposure in the liver and reduced circulating bile acid levels. Seladelpar also has positive effects on serum lipids, inflammation and fibrosis. Pruritus is a common symptom in patients with primary biliary cholangitis (PBC), but its origins are not completely understood. Both bile acids and interleukin-31 (IL-31) are thought to be involved in pruritus. Seladelpar treatment has been shown to reduce pruritus which was associated with decreased serum bile acids and IL-31.
	Important information about its composition: None
Hyperlink to the product information:	Lyvdelzi Summary of Product Characteristics (SmPC)
Indication(s) in the EEA:	Current: Lyvdelzi is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.
	Proposed (if applicable): Not applicable
Dosage in the EEA:	Current: 10mg/ day
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths:	Current (if applicable): Hard capsules, 10 mg
	Proposed (if applicable): Not applicable
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. Primary Biliary Cholangitis

SI.1.1. Incidence

A systematic review and meta-analysis showed the pooled global incidence of PBC was 1.76 per 100,000 persons/year (95% confidence interval (CI): 1.53-1.99). The pooled annual incidence was highest in North America (2.75/100,000) followed by Europe (1.86/100,000) and the lowest in the Asia-Pacific region (0.84/100,000). The incidence in Europe varied between Eastern Europe (0.77/100,000), Western Europe (2.26/100,000), Northern Europe (1.83/100,000) and Southern Europe (2.09/100,000) {Lv 2021, Trivedi 2021}.

Temporal trends showed the global incidence to be increasing until the year 2000 with rates then plateauing (incidence in North America, Europe and Asia-Pacific region in 1991-2000: 3.51, 2.28, and 0.69 respectively; and in 2011-2020: 2.95,2.61 and 0.86 respectively) although it should be noted that Asia-Pacific rates were not clearly reported until 1999 {Lv 2021, Trivedi 2021}.

SI.1.2. Prevalence

The pooled global prevalence has been estimated at 14.60 per 100,000 persons (95% CI: 12.64-16.56) with variation across studies from 1.91 to 40.2 per 100,000 persons. The highest prevalence was observed in North America (21.8/100,000) followed by Europe (14.6/100,000) and Asia-Pacific (9.8/100,000){Lv 2021, Trivedi 2021}. The prevalence of PBC in all three regions has risen steadily over time and data suggests a faster increase in North America compared to Europe {Lv 2021} .

SI.1.3. Demographics of the Population in the Approved Indication

Gender: The incidence and prevalence in females were found to be higher than that in males; the female to male prevalence ratio in the Asia-Pacific region was higher (approximately 90% female) than that in Europe and North America (approximately 70-90% female) {Lv 2021, Trivedi 2021}.

Age: PBC is exclusively a disease of adults. Most patients with the disease fall between the ages of 40-70, and prevalence has been shown to decline after the age of 70 {Lu 2018}.

Young presenting age is associated with more symptomatic disease and non-response to therapy. The Global PBC Study Group showed that biochemical response rate to first-line therapy with UDCA was < 50% for patient groups diagnosed at an age of <40 years compared with >80% for older patients {Trivedi 2021}.

Race: Roberts et al studied a Canadian cohort of 1538 patients with PBC which was comprised of 82% White, 4.7% Indigenous, 5.5% East Asian, 2.6% South Asian, and 5.1% miscellaneous ethnicities. This study indicated that Indigenous Canadians with PBC present with advanced disease and have worse long-term outcomes compared to White patients {Roberts 2022}.

Risk factors: The exact etiology of PBC is unknown, but genetic/epigenetic, environmental and immunological factors are thought to play a role.

Environmental factors, such as cigarette smoking, toxin exposure, and infectious agents, may breakdown the immune tolerance in individuals with genetic susceptibility {You 2022}.

Recently, genome-wide association studies (GWAS) have identified multiple genes conferring PBC susceptibility in human leucocyte antigen (HLA) and non-HLA loci. Studies have shown that HLA DRB1*11 and HLA-DRB1*13 are protective against PBC in European cohorts, whereas HLA-DQB1*06:04 and DQB1*03:01 are protective against the disease in Japanese cohorts. In Chinese Han, HLA-DQB1*03:01 confers PBC resistance, whereas HLA-DRB1*08:03 and HLA-DPB1*17:01 confer PBC susceptibility. Moreover, it is reported that HLA-DRB1*03:01 was significantly associated with anti sp100 positive sub-phenotype of PBC in Chinese Han. One of the significant non-HLA genes revealed by the GWAS is the interleukin-12 (IL-12) pathway {You 2022}.

SI.1.4. Main Existing Treatment Options

Ursodeoxycholic acid (UDCA) is the first-line treatment for PBC. It has been shown to improve overall transplant-free survival in PBC and has been the mainstay of treatment for many years. It is effective in approximately 60% of patients depending upon the definition of treatment response {De Vincentis 2022}. Intolerance to UDCA may also occur and is seen in up to 5% of patients {Invernizzi 2017}.

Ocaliva (OCA), a synthetic analogue of chenodeoxycholic acid, was conditionally approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2016 based on clinically notable decreases in alkaline phosphatase (ALP) levels while maintaining normal total bilirubin levels in subjects with PBC who have an inadequate response to UDCA or as a monotherapy in subjects with PBC who are intolerant to UDCA. In 2024, OCA's conditional approval was revoked in the EU and in the US the FDA issued a Complete Response Letter that it could not approve the supplementary New Drug Application seeking full approval. However, OCA currently remains available in the US under accelerated approval.

In June 2024, elafibranor, a pan-PPAR agonist, was granted accelerated approval in the US for treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA {IQIRVO and Ipsen Biopharmaceuticals Inc. 2024}, this followed by the conditional marketing authorization in the EU in September 2024 for the same indication {Iqirvo 2024}.

Approved anticholestatic treatments, including UDCA, OCA and elafibranor have shown no statistically significant benefit on pre-specified endpoints measuring pruritus. There are multiple off label treatments for cholestatic pruritus which are used in practice but do not have established efficacy and carry the risk of side effects.

Table SI.1. Risks associated with treatment options for PBC

Drug	Main risks
UDCA	Decompensation of hepatic cirrhosis, diarrhea, and use in pregnancy {UDCA 2023}
Elafibranor	Liver related events Elevated blood creatine phosphokinase and muscle injury (including patients on concomitant HMG-CoA reductase inhibitors) Embryo-foetal toxicity {Iqirvo 2024}

SI.1.5. Natural History of the Indicated Condition Including Mortality and Morbidity

Mortality:

PBC has been recognized since at least 1851. Initially the condition was known as "primary biliary cirrhosis" but as cirrhosis is only a feature of advanced disease, the name was changed in 2014 to "primary biliary cholangitis".

At initial diagnosis, most patients have both asymptomatic liver dysfunction and antimitochondrial antibodies. At onset, there is a silent phase with no liver dysfunction and only minute changes in liver histology, followed by a long period of asymptomatic liver dysfunction and, eventually, cirrhosis and end-stage liver failure. For patients diagnosed with cirrhosis, the median time to liver transplantation or death is 6–10 years without any intervention. The use of UDCA significantly improves survival in the majority of patients with PBC, with some reports suggesting a median survival time of 16–20 years. However, although the use of UDCA improves liver dysfunction, approximately one-third of patients are still at risk of progression to cirrhosis {Hasegawa 2021}. There is increasing understanding of the importance of ALP normalization, as elevation above the upper limit of normal (ULN) is associated with increased risk of clinical outcomes such as death and liver transplantation {Murillo Perez 2020}.

Morbidity:

Pruritus and fatigue are the most common presenting symptoms {European Association for the Study of the Liver. Electronic address 2017}. Cholestatic pruritus, the precise cause of which is uncertain, affects up to 70% of patients {Carey 2015}and can be extremely debilitating {Rishe 2008}. Severe pruritus causes sleep deprivation, social isolation, and can trigger suicidal ideation; in extreme cases, it can be an indication for liver transplantation even in the absence of liver failure symptoms {European Association for the Study of the Liver. Electronic address 2017}. Fatigue has been noted in up to 78% of patients and can be a clinically important cause of disability leading to a significant negative impact on quality of life {European Association for the Study of the Liver. Electronic address 2017, Lindor 2019}. The severity of fatigue is independent of the severity of the liver disease, and there is no proven treatment {European Association for the Study of the Liver. Electronic address 2017}.

Hepatomegaly, splenomegaly, and abdominal pain are also common in PBC patients. Portal hypertension (PHT) is a late complication of the disease {European Association for the Study of the Liver. Electronic address 2017, Lindor 2019} and has been reported to develop in PBC before the onset of cirrhosis. PBC disease progression can lead to cirrhosis and its sequelae, including worsening PHT, ascites, jaundice, and increased risk of hepatocellular carcinoma.

SI.1.6. Important Comorbidities

As with other autoimmune liver diseases, PBC is associated with concomitant extrahepatic autoimmune diseases. In a study by Karakaya et al, of 134 patients with PBC, 30 (22.4%) had concomitant autoimmune thyroid disease, 22 (16.4%) had Sjogren syndrome, 5 (3.7%) had rheumatoid arthritis, 5 (3.7%) had Type I diabetes and 3 (2.2%) had coeliac disease {Karakaya 2021}.

Liang et al conducted a meta-analysis to examine the association of PBC with cancer by meta-analysis. Compared with the general population, PBC patients, as compared to patients without PBC, had a significantly higher risk of overall cancer (pooled rate ratio [RR], 1.55; 95% CI, 1.28-1.83) and hepatocellular carcinoma (HCC) (pooled RR, 18.80; 95% CI, 10.81-26.79) in particular. It was not possible to draw a consistent conclusion about the association of PBC with the risks of stomach and pancreatic cancers. There was no significant association between PBC and breast cancer risk {Liang 2012}.

Patients with PBC have been reported to be at increased risk of osteoporosis in some studies. Risk factors for osteoporosis in PBC are older age, lower body mass index, severity of cholestasis, and advanced histological stage. Patients who have advanced stage PBC have a five-fold increase in risk for developing osteoporosis compared with those who have early-stage disease {Al-Harthy 2012}. Osteopenia and osteoporosis are more common among patients with PBC than the general population {Lindor 2019}. In a recent cohort study of 3,980 Swedish patients with PBC (median age 64 years), the annual fracture incidence was 4.9%, almost double that of age-matched controls, with a 5-year cumulative incidence of 16.8% in PBC patients vs 11.6% in age-matched controls {Schonau 2023}. In women with PBC, the annual incidence of fractures was 5.2%. The estimated incidence of osteoporotic fractures among people with PBC in this study was 2.81 per 100 patient-years.

Hyperlipidemia in patients with PBC is common with elevations in total cholesterol, LDL-cholesterol, triglycerides and HDL-cholesterol {Sorokin 2007}. Early studies did not establish an increased cardiovascular risk in PBC {Crippin 1992, Longo 2002}, although large definitive studies are difficult in this rare disease. Treatments with lipid lowering drugs improve lipid profiles in PBC {Cash 2013}.

PART II: MODULE SII—NONCLINICAL PART OF THE SAFETY SPECIFICATION

The pharmacological and toxicological effects of seladelpar vary according to its potency and selectivity towards the PPARδ, peroxisome proliferator receptor alpha (PPARα) and peroxisome proliferator receptor gamma (PPARγ) receptors, which in turn vary across humans and animal species. Seladelpar is highly selective for PPARδ in humans, with an ~630-fold and >2850-fold greater potency for PPARδ compared with PPARα or PPARγ, respectively. Seladelpar is less potent in activation of PPARδ in monkeys (~10 fold) and rats (~200-fold) than compared with humans. Additionally, seladelpar has weak activation of PPARα in monkeys and of PPARα and PPARγ in rats and mice but does not activate PPARγ in monkeys nor PPARα or PPARγ in humans at clinically relevant exposures.

Table SII.1. Table of Key Safety Findings From Nonclinical Studies

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Toxicity	
Key issues identified from acute or repeat-dose toxicity studies	
Single-Dose Toxicology Adverse signs and mortality were observed in mice at ≥ 50 mg/kg intra-peritoneal (IP) and in male rats at ≥ 62.5 mg/kg IP and female rats at ≥ 125 mg/kg IP. Oral administration was tolerated without clinical signs in mice at up to 1000 mg/kg. In rats, a single oral administration of seladelpar at ≥ 500 mg/kg was associated with dose-dependent clinical findings consisting of distended stomach, discoloured gastrointestinal (GI) tract (red) and/or stomach pyloric region (black), decreased activity, ataxia, ptosis, hunched posture and cold to touch.	The non-clinical findings are not considered to be a safety concern for humans at the proposed therapeutic dose.
Repeat Dose Toxicology	
Liver Hepatocellular necrosis was observed in male rats receiving 50 mg/kg/day in the 26-week study, in male monkeys receiving ≥ 5 mg/kg/day for 52 weeks, and in female mice given ≥ 25 mg/kg/day for 13 weeks. The necrosis in rats and mice was multifocal in the affected animals and minimal to mild in severity. There was complete recovery of the hepatic lesions in rats (reversibility was not evaluated in mice). In the affected monkeys, hepatocellular necrosis was minimal in severity and reversible. In the 52-week monkey study, the no-observed-adverse-event-level (NOAEL) was 1 mg/kg/day for males and 5 mg/kg/day in females due to adverse hepatocellular necrosis at higher doses.	The liver findings in monkeys occurred at exposures corresponding to an exposure margin 2.2- fold over the human area under the curve (AUC) 0-24hr (1095 ng·h/mL) at the 10 mg/day clinical dose. The liver changes in rats and mice demonstrated a correlation with seladelpar induced PPARα activation. Electron microscope (EM) evaluation demonstrated peroxisome proliferation in liver and kidney and induction of CYP4A and fatty acyl-coenzyme A (FCoA) in the rat 26-week study at ≥ 5 mg/kg/day, consistent with PPARα activation. In monkeys, peroxisome proliferation was also apparent by EM evaluation in liver and kidney, and hepatic CYP4A and FCoA were induced at as low as 1 mg/kg/day, consistent with PPARα agonism.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
	Collectively, these data are consistent with a PPARα-mediated mechanism for the liver changes in animal studies and, therefore, suggest a relatively lower risk for liver toxicity in humans given the 630-fold lower affinity of seladelpar for human PPARα (EC50, 1.26 μM) compared to PPARδ (EC50, 0.002 μM) in cell-based reporter gene assays. Whilst non-clinical findings indicate that the liver effects are seen at doses above the proposed human therapeutic dose and are due to the PPARα agonism, in clinical studies, transaminase elevations were seen at 200 mg and 50 mg doses with some shifts in transaminases at the 10 mg dose. For this reason, hepatotoxicity will be considered an Important Potential Risk.
Skeletal Muscle Minimal to moderate, reversible skeletal muscle degeneration was observed in female rats receiving 50 and 80 mg/kg/day in the 13-week study, in monkeys receiving 50 mg/kg/day for 13 weeks, in mice given ≥ 25 mg/kg/day for 13 weeks and in dogs given ≥ 5 mg/kg/day for 4 weeks. There were no treatment related histopathological findings of skeletal muscle degeneration in the monkey 52-week study.	Doses in which skeletal muscle effects were seen in non-clinical studies were at least 39.5 times the proposed therapeutic dose in humans. In addition, in clinical studies at doses of 10 mg there have not been any reports of myopathy or rhabdomyolysis. The non-clinical findings are not considered to be a safety concern for humans at the proposed therapeutic dose.
Cardiac Muscle Minimal to slight cardiac muscle degeneration was observed in male rats given ≥10 mg/kg/day in the 13-week toxicity study and progressive cardiomyopathy was noted in 50 mg/kg/day males in the 26-week rat study. Cardiac muscle degeneration was not observed in mice dosed for 13 weeks or in monkeys dosed for up to 52 weeks, despite mean drug exposures up to 277-fold higher than mean exposures in subjects treated with 10 mg/day. No cardiac muscle degeneration was observed in the monkey at doses up to 50 mg/kg/day, and histomorphometric data did not reveal any changes in the size of heart structures in chronic studies in rats through 26 weeks or in monkey through 52 weeks.	The lowest-observed-adverse-effect-level (LOAEL) for cardiac lesions in male and female rats treated for 13 weeks was 10.1-fold higher than the mean steady-state exposure in subjects given 10 mg/day seladelpar. However, the available data suggest that the cardiac muscle degeneration observed in rats is an exacerbation of age-related cardiomyopathy seen in this species{Chanut 2013}. During the 2-year carcinogenicity study, cardiomyopathy was observed at similar incidence across control and treated groups in males and most of the control male rats developed cardiac degenerative lesions during the study. In females, the incidence of cardiac degenerative lesions in control animals was higher than that observed in any seladelpar treatment group. Therefore, not only is cardiac muscle degeneration considered to be an exacerbation of a rat-specific change but, as a PPARα-dependent effect, is expected to have a lower chance of occurring after seladelpar exposure in humans, where activity against PPARα is much lower than activity against PPARδ. In clinical studies, there have not been any reports suggestive of cardiac muscle toxicity. The non-clinical findings are not considered to be a safety concern for humans.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Bone Marrow and Red Blood Cell Parameters Dose-related reductions in red blood cell mass (red blood cells [RBC], HB [haemoglobin] and HCT [haematocrit]) with corresponding decreases in reticulocyte counts were observed in rats, mice, monkeys, and dogs following repeated dosing with seladelpar.	The low red cell mass in combination with low reticulocyte counts are indications of decreased erythropoiesis. These occurred at doses of at least 35 times the proposed therapeutic dose in humans. In pivotal study CB8025-32048, mean values for selected hematology parameters at baseline were similar between treatment groups and remained generally unchanged at all postbaseline timepoints. The non-clinical findings are not considered to be a safety concern for humans.
Oesophagus and Stomach Epithelial hyperkeratosis of the non-glandular stomach and oesophagus was observed in rats following repeated dosing (14 days to 26 weeks dosing), which is considered a rodent-specific finding in response to irritation {Proctor 2007}. Similar findings were not observed in dogs at dosing durations of up to 4 weeks or monkeys at dosing durations up to 52 weeks and at higher systemic exposures. In particular, in the 52-week monkey toxicity study, a lack of cell proliferation was confirmed in the oesophagus by immunochemistry. Therefore, epithelial hyperkeratosis of the non-glandular stomach and esophagus is considered to be a rat-specific finding and not relevant for human risk.	The epithelial hyperkeratosis of the non-glandular stomach and esophagus is considered to be a rat-specific finding and not relevant for human risk.
Reproductive/developmental toxicity	
Seladelpar did not affect fertility in male or female rats at doses up to 100 mg/kg/day. In pregnant rats and rabbits, seladelpar was not teratogenic and had no effects on embryo-foetal survival. In pregnant rabbits, the administration of 40 mg/kg/day (40.6-fold above the clinical AUC) was associated with reduced maternal and foetal body weights, but no foetal anomalies. In pregnant and lactating female rats, the administration of 100 mg/kg/day (145.2-fold above the clinical AUC) was associated with reduced maternal food consumption and body weight gain. The first filial (F1) generation offspring had reduced survival and body weight gain during the lactation period, with associated delays in developmental milestones at this dose. Although body weight decrements persisted during the post-weaning period, the rate of weight gain was comparable. No effects on postnatal development were seen at the next lowest dose of 20 mg/kg/day (15.2-fold above the clinical AUC).	In animal developmental toxicity studies, effects on foetal and post-natal growth were observed at > 40-fold exposure compared to seladelpar 10mg and hence clinical risk is low. Use in Pregnancy will be considered Missing Information in this RMP.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Genotoxicity	
Seladelpar was negative for genotoxicity in bacterial and mammalian in vitro assays, and in an in vivo mouse bone marrow micronucleus assay.	No safety concern relevant to human use has arisen from these non-clinical data.
Carcinogenicity	
Seladelpar was evaluated for carcinogenic potential in 2-year rat (Sprague-Dawley) and mouse (CD-1) cancer bioassays at plasma exposure (AUC) margins up to 22-fold (female rats), 65-fold (male rats), 82-fold (male mice), and 115-fold (female mice) relative to exposures at the highest daily dose targeted for the clinical development program of 10 mg/day. Tumours considered treatment-related were observed in liver and forestomach in both species, and in the testis and pancreas of high-dose male rats only.	Tumours of the non-glandular stomach, which were observed at low incidences are not considered relevant to cancer risk in humans, particularly when test articles are administered by gavage {Proctor 2007}. The combination of liver tumours in mice and liver, pancreas and testis tumours in rats is characteristic of PPARα activation {Klaunig 2003} and these tumours in seladelpar-treated animals likely resulted from PPARα agonism. To confirm this hypothesis, extensive investigations were undertaken to evaluate the mechanism of action (MOA) of liver tumours in mice and rats given seladelpar, which provided strong evidence that liver tumours were produced through PPARα activation. Important key events in the MOA leading to liver tumours in rodents included seladelpar activation of PPARα, perturbed hepatocyte growth, and subsequent selective clonal expansion leading to tumour formation. Further evidence was generated to support a PPARα-dependent process including induction of PPARα-regulated genes, peroxisome proliferation and associated oxidative stress, induction of CYP4A and acetyl coenzyme A (CoA) oxidase, and liver cell hypertrophy, all of which are known PPARα-driven events. This MOA for PPARα agonists has previously been demonstrated to directly result in liver tumour formation in mice and rats (mouse being the more sensitive species), and to indirectly result in Leydig cell and pancreatic acinar cell tumours in rats {Klaunig 2003}, a spectrum of neoplasia corresponding to the PPARα-driven tumour responses induced by seladelpar in the rodent carcinogenicity studies. Seladelpar did not induce PPARα-mediated peroxisomal gene expression or enzyme induction in human hepatocytes at up 10 µM, considerably above clinical therapeutic Cmax. The non-clinical findings in rodents are not considered to be a safety concern for humans.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Safety pharmacology	
Cardiovascular system, including potential effect on the QT interval	
Seladelpar did not cause any changes in safety pharmacology parameters related to cardiovascular function in in vitro or in vivo studies, including a GLP cardiovascular (and respiratory) study in conscious dogs at up to 80 mg/kg. The hERG safety margin for clinical Cmax as free seladelpar was >857. In addition, no seladelpar-related changes in PR interval, QRS duration, QT interval, corrected QT (QTc) interval, or heart rate were observed on Day 91, 181, or 360 of the dosing phase in males given 1, 5, or 25/12.5 mg/kg/day or females given 1, 5, or 25/12.5/8 mg/kg/day for up to 52 weeks in a 1-year general toxicity study in monkeys. No rhythm abnormalities or qualitative electrocardiogram (ECG) changes were attributed to seladelpar during qualitative assessment of the ECGs.	In a Phase 1 study designed to assess the cardiac conduction effect of a single oral dose of seladelpar 10 or 200 mg compared to placebo (Study CB8025-11733), concentration regression analysis indicated that seladelpar was not associated with significant QT prolongation when administered in single doses up to 200 mg. No safety concern relevant to human use has arisen from these clinical data and as supported by the non-clinical in vitro and in vivo cardiovascular studies.
Nervous system	
Seladelpar did not cause any changes in safety pharmacology parameters related to the nervous system.	No safety concern relevant to human use has arisen from these non-clinical data.
Respiratory system	
Seladelpar did not cause any changes in safety pharmacology parameters related to respiratory function.	No safety concern relevant to human use has arisen from these non-clinical data.
Other toxicity-related information or data	
None	

Table SII.2. Safety concerns from non-clinical data

Important identified risks	None
Important potential risks	Hepatotoxicity
Missing information	Use in Pregnancy

PART II: MODULE SIII —CLINICAL STUDY EXPOSURE

SIII.1. Clinical Study Exposure

The tables in this section present exposure data to seladelpar as of 13 February 2025 in patients with PBC from the following studies:

- Completed studies
  - CB8025-21528, CB8025-21629, CB8025-31735, CB8025-32048
- Ongoing blinded
  - CB8025-32251, CB8025-41837
- Ongoing open label
  - CB8025-31731-RE, CB8025-31838* (*this study is now completed)

Table SIII.1. Duration of Exposure for All Indications and Patients with PBC

Cumulative for All Indications				
	Ongoing Blinded Studies (All Participants Treated)		**Completed or Ongoing Open Label Studies (Participants exposed to Seladelpar)**	
Duration of Exposure	**Number of Participants**	**Person-days**	**Number of Participants**	**Person-days**
≥ 1 Day	131	27379	1187	507240
≥ 30 Days	123	27314	813	505452
≥ 90 Days	97	25784	635	494962
≥ 180 Days	70	22368	591	488958
≥ 1 Year	17	7511	465	450028
≥ 2 Years	0	0	290	365639
≥ 3 Years	0	0	159	241437
PBC				
	Ongoing Blinded Studies (All Participants Treated)		**Completed or Ongoing Open Label Studies (Participants exposed to Seladelpar)**	
Duration of Exposure	**Number of Participants**	**Person-days**	**Number of Participants**	**Person-days**
≥ 1 Day	131	27379	561	446624
≥ 30 Days	123	27314	529	446069
≥ 90 Days	97	25784	488	443712

Cumulative for All Indications				
	Ongoing Blinded Studies (All Participants Treated)		Completed or Ongoing Open Label Studies (Participants exposed to Seladelpar)	
Duration of Exposure	Number of Participants	Person-days	Number of Participants	Person-days
≥ 180 Days	70	22368	448	438226
≥ 1 Year	17	7511	403	426759
≥ 2 Years	0	0	290	365639
≥ 3 Years	0	0	159	241437

Cumulative exposure up to 13 February 2025 was summarized
Duration of Exposure = Last dose date – First dose date + 1
Person-days is defined as the number of days each participant was on seladelpar or blinded treatment for ongoing blinded studies. Ongoing blinded studies include all participants enrolled in the study and entered in the clinical database as the time of the data snapshot date. Studies with finalized database available are considered completed.

Table SIII.2. Exposure by Age Group and Gender in PBC patients

	Ongoing Blinded Studies (All Participants Treated)		Completed or Ongoing Open Label Studies (Participants exposed to Seladelpar)	
Gender and Age Group	Number of Participants	Person-days	Number of Participants	Person-days
Female				
< 16 Years	0	0	0	0
16-25 Years	0	0	0	0
26-35 Years	0	0	13	7247
36-45 Years	7	1350	46	37851
46-55 Years	27	6211	183	141949
56-65 Years	50	9494	199	158777
66-75 Years	36	8110	85	74107
> 75 Years	1	35	2	1357
Missing	0	0	0	0
Male				
< 16 Years	0	0	0	0
16-25 Years	0	0	0	0
26-35 Years	0	0	0	0
36-45 Years	1	164	3	2668
46-55 Years	1	289	12	9090
56-65 Years	4	789	8	4353

Gender and Age Group	Ongoing Blinded Studies (All Participants Treated)		Completed or Ongoing Open Label Studies (Participants exposed to Seladelpar)	
	Number of Participants	Person-days	Number of Participants	Person-days
66-75 Years	3	815	9	8213
> 75 Years	1	122	1	1012
Missing	0	0	0	0

Cumulative exposure up to 13 February 2025 was summarized
Duration of Exposure = Last dose date – First dose date + 1
Person-days is defined as the number of days each participant was on seladelpar or blinded treatment for ongoing blinded studies. Ongoing blinded studies include all participants enrolled in the study and entered in the clinical database as the time of the data snapshot date. Studies with finalized database available are considered completed.

Table SIII.3. Exposure by Race in Patients With PBC

Race	Ongoing Blinded Studies (All Participants Treated)		Completed or Ongoing Open Label Studies (Participants exposed to Seladelpar)	
	Number of Participants	Person-days	Number of Participants	Person-days
White	102	22402	497	397506
Black or African American	5	786	15	10246
Asian	19	3707	36	31634
American Indian or Alaska Native	0	0	8	3847
Native Hawaiian or Other Pacific Islander	0	0	0	0
Other	2	113	1	1304
Not Permitted	0	0	0	0
Multiple	1	213	1	541
Missing	1	53	3	1546
Not Reported	1	105	0	0

Cumulative exposure up to 13 February 2025 was summarized
Duration of Exposure = Last dose date – First dose date + 1
Person-days is defined as the number of days each participant was on seladelpar or blinded treatment for ongoing blinded studies. Ongoing blinded studies include all participants enrolled in the study and entered in the clinical database as the time of the data snapshot date. Studies with finalized database available are considered completed.

PART II: MODULE SIV—POPULATIONS NOT STUDIED IN CLINICAL STUDIES

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Advanced PBC as defined by the Rotterdam criteria (albumin below the lower limit of normal and total bilirubin above 1.0 × ULN)	These patients were excluded for safety reasons due to lack of dose ranging and safety experience in PBC patients with advanced disease.	**No** **Rationale:** The laboratory findings that define Advanced PBC by Rotterdam criteria may be seen in patients with severe (Child Pugh C) hepatic impairment (a population not recommended in the SmPC). The uncertain benefit of using seladelpar in patients with decompensated cirrhosis would be recognised by clinicians and is not recommended. Therefore, this is not considered missing information. These laboratory findings may also be seen in patients with moderate (Child Pugh B) hepatic impairment, which is considered missing information.
Presence of clinically important hepatic decompensation, including: • History of liver transplantation, current placement on liver transplantation list, or current Model for End-Stage Liver Disease (MELD) score ≥12 • Complications of portal hypertension, including known oesophageal varices, history of variceal bleeds or related interventions, ascites, and hepatic encephalopathy • Cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis	These patients were excluded for safety reasons due to limited dose ranging and safety experience in PBC patients with advanced disease.	**No** **Rationale:** The uncertain benefit of using seladelpar in patients with decompensated cirrhosis would be recognised by clinicians. Therefore, use in these populations is not considered missing information

Criterion	Reason for Exclusion	Considered to be Missing Information
Current features of autoimmune hepatitis (AIH) as determined by the Investigator based on immunoserology, liver biochemistry or historic confirmed liver histology	Defining a population without AIH and specifically AIH-PBC overlap syndrome was important to avoid confounding the results. Use of steroids to treat AIH was also excluded so as not to confound the assessment of safety of seladelpar.	**No** **Rationale:** AIH is not an indicated population; AIH-PBC overlap is not an indicated population. These patients are unlikely to be treated with seladelpar. Given the rarity of the overlap of PBC and AIH, there are no plans to study this patient population and the benefit of seladelpar use is uncertain. Therefore, use in these populations is not considered missing information.
Primary sclerosing cholangitis	Preence of other concomitant liver conditions would not allow for reliable assessment of efficiency and safety in PBC.	**No** **Rationale:** PSC is not an indicated population. These patients have a different pattern of liver disease characteristics (bile duct strictures), co-morbidities (cholangiocarcinoma and inflammatory bowel disease). Seladelpar is not indicated in this patient population. Therefore, use in this population is not considered missing information.
History or clinical evidence of alcoholic liver disease Known history of alpha-1-antitrypsin deficiency History or evidence of Gilbert's syndrome with elevated total bilirubin History or evidence of haemochromatosis Hepatitis B, defined as the presence of hepatitis B surface antigen (HBsAg) at screening Hepatitis C, defined as the presence of hepatitis C virus (HCV) ribonucleic acid (RNA) at screening	Presence of other concomitant liver conditions would not allow for reliable assessment of efficacy and safety of seladelpar in PBC	**No** **Rationale:** While it is not expected that seladelpar would mechanistically work differently in these populations, the evaluation of efficacy of treatment would be confounded by the additional liver disease, which is recognized by treating physicians. Therefore, use in these populations is not considered missing information.
Known history of HIV (human immunodeficiency virus) or positive antibody testing	To avoid confounding evaluation of efficacy and safety outcomes. HIV infections might advance progression of liver disease. Comorbidities of HIV and medications for HIV may interfere with assessing of safety data.	**No** **Rationale:** The safety profile is not expected to differ from the known safety profile.

Criterion	Reason for Exclusion	Considered to be Missing Information
Clinically important alcohol consumption	Alcohol consumption during the course of the study would have confounded safety and efficacy evaluations due to impact on liver function.	**No** **Rationale:** The product labeling provides adequate advice regarding liver function monitoring. Furthermore, in normal clinical practice, physicians understand the need for additional monitoring of liver function in patients with significant alcohol consumption. The safety in this population can therefore be monitored and no further studies in this patient population are deemed feasible or necessary.
History of malignancy diagnosed or treated, actively or within 2 years, or ongoing evaluation for malignancy; localised treatment of squamous or noninvasive basal cell skin cancers and cervical carcinoma in situ is allowed if appropriately treated prior to screening	Excluded to ensure that a subject with a pre-disposition to cancer or active cancer would not confound the evaluation of seladelpar safety.	**No** **Rationale:** The uncertain benefit of using seladelpar in these patients would be recognised by clinicians. Patients with recent or ongoing malignancy will be treated for their malignancy as their primary condition. It is not expected that seladelpar would mechanistically work differently in these populations or have a different safety profile. The evaluation of efficacy of treatment might be confounded and recognized by treating physicians.
Treatment with OCA and/or fibrates 6 weeks prior to screening	Fibrates are used off label to treat PBC and were excluded to avoid confounding evaluation of efficacy and safety outcomes. OCA was an approved treatment for PBC and was excluded to avoid confounding evaluation of efficacy and safety outcomes.	**No** **Rationale:** Treatment with concomitant seladelpar and OCA and/or fibrates is not expected in the post marketing period according to expected clinical practice. Safety of seladelpar is not expected to differ if fibrates or OCA are used prior to seladelpar treatment.
Treatment with colchicine, methotrexate, azathioprine or long terms systemic steroids (> 2 weeks) during two months prior to screening	To avoid confounding evaluation of efficacy and safety outcomes. These medicines have a significant anti-inflammatory or immunomodulatory effect, therefore confounding the assessment of the anti-inflammatory effect from seladelpar.	**No** **Rationale:** Recommendations regarding drug interactions is provided in the SmPC. The safety profile is not expected to differ from the known safety profile.
Immunosuppressant therapies (eg, cyclosporine, tacrolimus, anti-tumor necrosis factor (TNF) or other immunosuppressive biologics)	To avoid confounding evaluation of efficacy and safety outcomes. Immunosuppressants have a significant anti-inflammatory or immunomodulatory effect and therefore could confound the seladelpar anti-inflammatory effect. These medications could mask any autoimmune component to a patient's liver disease or	**No** **Rationale:** In a dedicated clinical drug interaction study, concomitant administration of 10 mg seladelpar (single dose) with cyclosporine, a BCRP inhibitor, resulted in an approximately 2.16-fold increase in the AUC0-∞ and 2.88-fold increase in Cmax of seladelpar. Concomitant administration of seladelpar with cyclosporine may result in an increase in seladelpar exposure. When seladelpar is concomitantly administered with cyclosporine patients should be closely monitored for adverse effects.

Criterion	Reason for Exclusion	Considered to be Missing Information
	confound the assessment of safety of seladelpar.	
Very elderly (>75 years)	Study population included adult participants aged 18 to 75 years old (inclusive)	**No** **Rationale:** The safety profile of seladelpar is not expected to differ in patients >75 years. Currently ongoing studies (ASSURE and AFFIRM) do not have an upper age limit for enrolment. Of note, other studies not in PBC (e.g., the renal impairment study CB8025-11942) did include some participants over 75. In Study CB8025-32048 there were 3 participants aged 75 at entry into the study (2 on seladelpar and 1 on placebo). As of 31 January 2024, there were further 4 participants who enrolled in CB8015-31731-RE aged ≥75 at entry into the study. As of 13 February 2025, there were 5 participants aged over 75 years old in ongoing and completed seladelpar PBC studies. While the number of participants in the age ≥75 subgroup is small, no safety signals were identified among those participants. It is expected that healthcare providers will recognize this as a population in which treatment decisions should be taken with consideration for co-morbidities and polypharmacy. Safety in participants aged 75 and over will continue to be monitored in ongoing seladelpar studies and through routine pharmacovigilance.
Pregnancy	Unknown safety profile for pregnant women. Study population included women of childbearing potential, but the protocol required a negative pregnancy test before study commenced. Pregnancy was a reason to terminate study prematurely.	**Yes**
Lactation	Breastfeeding women were excluded from the study population. It is unknown if seladelpar is excreted in milk, therefore the effect on the breastfed child remains unknown.	**No** **Rationale:** No cases of breast-feeding while on treatment have been reported in seladelpar clinical development. Due to the patient demographics, the exposure during breast feeding in post-marketing setting is expected to be very low, if any. However, as a precautionary measure, the SmPC includes information that it is unknown whether seladelpar or its metabolites are excreted in human milk. A risk to the newborns/ infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from seladelpar therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Study Development Programs

Table SIV.2. Ability of the Clinical Study Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Study Program	Discussion of Implications for Target Population
Which are rare	Over 600 participants with PBC were exposed to seladelpar in the clinical studies (as of 13 Feb 2025).	ADRs occurring at greater than 0.6% are likely to have been seen (based on Rule of 3)
Due to prolonged exposure	Nearly 300 participants have been treated with seladelpar for over 2 years and more than 150 for over 3 years (as of 13 Feb 2025)	No ADRs specifically associated with prolonged exposure have been identified in the clinical trial program.
Due to cumulative effects	Nearly 300 participants have been treated with seladelpar for over 2 years and more than 150 for over 3 years (as of 13 Feb 2025)	No cumulative effects have been identified in the clinical trial program.
Which have a long latency	Nearly 300 participants have been treated with seladelpar for over 2 years and more than 150 for over 3 years (as of 13 Feb 2025)	No long latency effects have been seen in the clinical trial program

SIV.3. Limitations in Respect to Populations Typically Underrepresented in Clinical Study Development Programs

Table SIV.3. Exposure of Special Populations Included or Not in Clinical Study Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with hepatic impairment	In study CB8025-11732, 8 participants in each of normal, mild, moderate and severe hepatic impairment (HI) were studied. Overall, single doses of 10 mg seladelpar were well-tolerated by participants with normal hepatic function and participants with varying degrees of HI in this study. In addition, study CB8025-21838 investigated the effect of seladelpar ≤ 10mg in patients with PBC and mild to severe HI. In each cohort of CP-A, CP-A+PHT, CP-B and CP-C, 6 patients were enrolled (24 in total). In study CB8025-32048, a total of 27 (14%) participants (14.1% and 13.8% of participants in the seladelpar and placebo groups, respectively) had cirrhosis at baseline.

Type of Special Population	Exposure
	In study CB8025-32048, a total of 25 (13.0%) participants (15.6% and 7.7% in the seladelpar and placebo groups, respectively), had total bilirubin > 1.0× ULN at baseline. As of the latest data cutoff of 31 Jan 2024, the subpopulation of participants with cirrhosis who received seladelpar 10 mg in Studies CB8025-32048 and CB8025-31731-RE comprised 62.
Patients with renal impairment	In study CB8025-11942, 8 participants with mild renal impairment (estimated glomerular filtration rate (eGFR) ≥60 to <90 mL/min/1.73 m^2), 8 participants with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2), and 8 participants with severe renal impairment (eGFR < 30 mL/min/1.73 m^2 and not on dialysis) were studied.
Population with relevant different ethnic origin (including race and ethnicity)	In study CB8025-32048, 89.1% of partricipants exposed to seladelpar were White. 1.6% were Black or African American, 5.5% were Asian and 2.3% were American Indian or Alaska Native. 22.7% were Hispanic or Latino. In study CB8025-31735 in the all seladelpar group, 89.9% were White. 2.8% were Black or African American, 6.7% were Asian and 0.6% American Indian or Alaska Native. 15.7% were Hispanic or Latino.
Subpopulations carrying relevant genetic polymorphisms	To determine the extent by which CYP2C8, CYP2C9, and uridine diphosphate (UDP) glucuronosyltransferase (UGT) 1A1 metabolic activity influence the exposure of seladelpar, an analysis was carried out using pooled data from three clinical pharmacology studies (CB8025-11840, CB8025-11941, and CB8025-11942). Overall, this analysis showed that seladelpar systemic levels were similar among CYP2C8, CYP2C9, UGT1A1 extensive metaboliser (EM), intermediate metaboliser (IM) and poor metaboliser (PM) subjects.
Immunocompromised patients	Not included in the clinical development program

PART II: MODULE SV—POSTAUTHORIZATION EXPERIENCE

SV.1. Post authorization Exposure

SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed seladelpar is estimated from sales data and is reported in periodic safety update reports (PSURs).

SV.1.2. Exposure

Cumulative patient exposure to marketed seladelpar, since first marketing approval in the US on 14 August 2024 to 13 February 2025 is estimated to be 323 patient years.

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

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for seladelpar to be misused 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. Risk(s) Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.1. Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reason	List of Risks
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Not applicable
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	Not applicable
Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU member state where the product is authorized)	Not applicable
Known risks that do not impact the risk-benefit profile	Headache
	Abdominal distension
	Abdominal pain
	Nausea
Other reasons for considering the risks not important:	Not applicable

EU = European Union

SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

There are no risks of seladelpar treatment that are considered to be Important Identified Risks.

SVII.1.2.2. Important Potential Risks

Table SVII.2. Important Potential Risks

Important Potential Risks	Risk-Benefit Impact
Hepatotoxicity	**Non-clinical findings**: Minimal, reversible, hepatocellular necrosis was observed in male rats receiving the highest dose of 50 mg/kg/day in the 26-week study and male monkeys receiving ≥5 mg/kg/day for 52 weeks. **Clinical findings:** Seladelpar has been associated with dose related increases in serum transaminases (AST and ALT) levels greater than 3 times upper limit of normal (ULN) in subjects with PBC receiving doses of 50 and 200 mg/day (5- and 20-times the recommended 10 mg/day dose). Transaminase levels returned to pretreatment levels upon treatment discontinuation. No pattern for increases in transaminases levels was observed at lower doses (2, 5 or 10 mg). **Risk-benefit impact:** The benefit of seladelpar as an effective treatment for PBC outweighs the potential risk of transaminase elevation. The SmPC states that dose dependent increases in serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) have been observed in patients receiving higher doses of seladelpar. The SmPC advises to obtain baseline clinical and laboratory assessments at initiation of treatment with seladelpar and monitor thereafter according to routine clinical practice. Consider temporary interruption of seladelpar treatment if liver tests worsen, or the patient develops signs and symptoms consistent with liver dysfunction. Consider permanent discontinuation if liver tests worsen again after restarting seladelpar.

SVII.1.2.3. Missing Information

Table SVII.3. Missing Information

Missing Information	Risk-Benefit Impact
Use in Pregnancy	**Non-clinical findings**: In pregnant rabbits, the administration of 40 mg/kg/day (40.6-fold above the clinical AUC) was associated with reduced maternal and foetal body weights, but no foetal anomalies. In pregnant and lactating female rats, the administration of 100 mg/kg/day (145.2-fold above the clinical AUC) was associated with reduced maternal food consumption and body weight gain. The first filial (F1) generation offspring had reduced survival and body weight gain during the lactation period, with associated delays in developmental milestones at this dose. Although body weight decrements persisted during the post-weaning period, the rate of weight gain was comparable. No effects on postnatal development were seen at the next lowest dose of 20 mg/kg/day (15.2-fold above the clinical AUC).

Missing Information	Risk-Benefit Impact
	Clinical and postmarketing experience: As per clinical study practice, pregnant participants were excluded from clinical studies with seladelpar. There are therefore limited data on the use of seladelpar in pregnant women. As of 13 February 2025, there were 5 pregnancies reported including 4 reported in seladelpar clinical program. The outcome of the 5 pregnancies was as follows: 2 therapeutic abortions, 2 unknown and 1 live birth. In the case of live birth, no congenital defects were reported. **Risk-benefit impact:** There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of seladelpar in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposure levels, however, as a precautionary measure, it is preferable to avoid the use of seladelpar during pregnancy.
Long term safety	**Clinical experience:** Due to the chronic nature of the condition, patients with PBC might require long term therapy with seladelpar and availability of data on safety of the long-term treatment, (> 2 years) is limited. The primary evidence of the safety of seladelpar in PBC is provided from the phase 3, double-blind, randomised, placebo-controlled study CB8025-32048 (RESPONSE) that evaluated oral seladelpar 10 mg once daily versus placebo over 52 weeks (12 months), further supported with data from study CB8025-31735 (ENHANCE), with the primary analysis at 3 months. At the time of submission there was limited experience beyond 2 years of continuous use. While available data indicate safety remains consistent with extended exposure, including exposure beyond 2 years, this will continue to be reflected as missing information while additional data accrue for ongoing studies. **Risk-benefit impact:** Throughout the clinical development in PBC patients, seladelpar 10 mg was found to improve pruritus, and biomarkers of cholestasis and liver injury, such as ALP, bilirubin, and ALT over 52 weeks. Through its development program, seladelpar was well tolerated and demonstrated a favorable safety profile across the population studied that continued to be favorable when used up to 2 years in the long-term open extension study. However, safety data in patients treated continuously for more than 2 years is limited. Long term safety of seladelpar therapy will continue to be monitored in ongoing clinical studies and through routine pharmacovigilance.

Missing Information	Risk-Benefit Impact
Use in PBC patients with moderate (Child Pugh B) hepatic impairment	**Clinical experience:** The seladelpar clinical development program in PBC included participants without cirrhosis and with compensated cirrhosis, nearly all CP-A; seladelpar appeared overall safe and well tolerated in patients across the population studied. Child Pugh B patients with compensated cirrhosis are included in the ongoing PBC Study CB8025-41837 (AFFIRM), However, limited data is still available for this patient population. There is possibility that liver disease, including more advanced cirrhosis, might slow drug metabolism. As a result, drug exposure may be increased resulting in possible changes to the safety profile of seladelpar in this patient population. Two PK studies for seladelpar have been conducted with the main aim to evaluate pharmacokinetics and metabolism of seladelpar in participants with varying degrees of hepatic impairment (Study CB8025-11732 and Study CB8025-21838). In study CB8025-21838, close to 2-fold increases in exposures were seen in participants with CP-A with portal hypertension or with CP-B cirrhosis and slightly above 2-fold increases in exposures were seen in participants with CP-C cirrhosis compared to participants with CP-A cirrhosis without PHT. No safety concerns related to seladelpar were identified, but data were available in a limited number of participants with repeated dosing of seladelpar ≤ 10 mg for 28 days. Use of seladelpar in PBC patients with moderate (Child Pugh B) hepatic impairment may be of interest to healthcare providers given limited treatment options in this population and the possibility of benefit, hence it is considered missing information. In contrast, in PBC patients who have severe (Child Pugh C) hepatic impairment, treatment with seladelpar is not expected due to understanding by treating clinicians of low likelihood of a treatment benefit (rather, these patients may be evaluated for liver transplant). Currently Section 4.2 of the SmPC includes the following information on use of seladelpar in patients with hepatic impairment: No dose adjustment is required in PBC patients with mild hepatic impairment (Child Pugh A). Safety and efficacy of seladelpar have not been established in PBC patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Consider discontinuing seladelpar if the patient progresses to moderate hepatic impairment. Use is not recommended in patients with severe hepatic impairment. **Risk-benefit impact:** Based on small numbers of patients enrolled and potential for higher exposures in the setting of advancing hepatic impairment, no conclusions could be made on the safety of seladelpar treatment in patients with moderate (Child Pugh B) hepatic impairment. Therefore, use in PBC patients with moderate (Child Pugh B) hepatic impairment is proposed to be included as missing information.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

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

SVII.3.1.1. Important Identified Risks

There are no important identified risks for seladelpar.

SVII.3.1.2. Important Potential Risks

Table SVII.4. Important Potential Risk

Important Potential Risk	Hepatotoxicity
Potential mechanisms	The mechanism for hepatocellular toxicity seen at high doses is not known.
Evidence source and strength of evidence	**Non-clinical findings:** Minimal, reversible, hepatocellular necrosis was observed in rats and monkeys. The liver findings in monkeys occurred at exposures corresponding to exposure margins 2.2- and 11-fold, respectively, over the human AUC 0-24 hr (1095 ng·h/mL) at the 10 mg/day clinical dose. In addition, the liver changes in rats and mice demonstrated a correlation between these changes and seladelpar induced PPARα activation. Additionally, EM evaluation demonstrated peroxisome proliferation in liver and kidney and induction of CYP4A and FCoA in the rat 26-week study at ≥ 5 mg/kg/day, consistent with PPARα activation. In monkeys, peroxisome proliferation was also apparent by EM evaluation in liver and kidney, and hepatic CYP4A and FCoA were induced at as low as 1 mg/kg/day, consistent with PPARα agonism. Collectively, these data are consistent with a PPARα-mediated mechanism for the liver changes in animal studies and, therefore, suggest a relatively lower risk for liver toxicity in humans given the 630-fold lower affinity of seladelpar for human PPARα (EC_{50}, 1.26 μM) compared to PPARδ (EC_{50}, 0.002 μM) in cell-based reporter gene assays.
Characterization of the risk	In Clinical Study CB8025-21528, increases in transaminases (AST and ALT) in subjects with PBC were observed specifically with seladelpar 50 and 200 mg/day. These elevations appeared to be dose dependent and specific to the PBC population to date. The increases were rapid (within 2 weeks), asymptomatic, and fully reversible upon treatment discontinuation. **<u>Treatment Emergent Adverse Events (TEAEs)</u>** **Study CB8025-32048 TEAEs** Liver-related TEAEs were defined using broad Hepatic disorders standardised MedDRA (Medical Dictionary for Regulatory Activities) query (SMQ).

Important Potential Risk	Hepatotoxicity
	In study CB8025-32048, 8 (6.3%) subjects in the seladelpar 10 mg group and 6 (9.2%) in the placebo group experienced a liver-related TEAE. The preferred terms included in this TEAE category were individually reported in each group with the exception of hepatic cirrhosis, which was reported for 3 (2.3%) subjects in the seladelpar group and 1 (1.5%) subject in the placebo group. Most liver-related TEAEs were Grade 1 or 2, with exception of a Grade 3 treatment-emergent SAE oesophageal varices haemorrhage that occurred in 1 subject of the seladelpar group in the setting of known cirrhosis at baseline. There were no other treatment-emergent SAEs reported in this category. **Study CB8025-31735 TEAEs** In supportive study CB8025-31735, liver events were defined as those TEAEs occurring in the hepatobiliary disorders System Organ Class (SOC). A total of 9 (3.4%) subjects had TEAEs in this SOC, including 3.4% of subjects in each treatment group; none reported Grade ≥ 3 or treatment-emergent serious adverse events (SAEs) in this SOC. The only TEAE in this SOC reported in ≥ 2% of subjects in any treatment group was portal vein occlusion (2 [2.2%] in the seladelpar 10 mg group, 1 [1.1%] in the placebo group). All 3 events occurred at the same site and were diagnosed solely based on findings in liver biopsies, which the Investigator performed post-treatment following the report of the findings in the NASH study. Given the events occurred in an equal number of seladelpar and placebo subjects, findings could be explained by PBC alone. There were no pre-treatment biopsies available, the Investigator and Sponsor assessed the events as unlikely related to study drug. Two subjects in the seladelpar 5 mg group had TEAEs in the hepatobiliary disorders SOC that were assessed as treatment-related by the Investigator, including 1 subject with Grade 2 hepatic fibrosis and 1 subject with Grade 1 hepatic cyst. **Uncontrolled studies TEAEs** As of 29 June 2023, liver-related TEAEs in study CB8025-31731-RE as identified by predefined search criteria were reported in 3.9% of subjects overall. All liver related TEAEs were Grade 1 or 2 in severity. The most common liver-related TEAEs for CB8025-31731-RE subjects in legacy and CB8025-21838 studies were AST increased (2.3%), ALT increased (1.7%), and blood bilirubin increased (1.1%). All other preferred terms were reported in 1 subject each. In study CB8025-31731, liver events were defined as those TEAEs occurring in the hepatobiliary disorders SOC. One (0.9%) subject experienced two TEAEs in this SOC: Grade 3 cholelithiasis and Grade 3 bile duct stone, both of which were considered unrelated to study drug (medical history included cholecystectomy, recurrent bile duct stones, repeated retrograde cholangiopancreatographies for recurrent choledocholithiasis and biliary cholic). **<u>Cholestatic Markers and Liver Enzymes</u>** **Liver Biochemistry Parameters Study CB8025-32048** Similar percentages of subjects in the seladelpar and placebo groups (7.0% vs 6.2%, respectively) had a shift of ≥ 2 severity grades in select liver biochemistry parameters; most were 2-grade shifts. The most frequently observed abnormal biochemistry laboratory parameter in this category was blood bilirubin increased (seladelpar 4.7% vs placebo 4.6%). One subject in the seladelpar group who had

Important Potential Risk	Hepatotoxicity
	cirrhosis at baseline had a 3-grade shift in total bilirubin. A gradual onset of laboratory value changes and concurrent worsening of cirrhosis was noted for this subject. **Liver Biochemistry Parameters in Uncontrolled Studies** In study CB8025-31731-RE, as of 29 June 2023, reported TEAEs identified by predefined search strategy for potentially reflecting liver-related toxicity were reported for 11 subjects (3.9%) in the Overall study population. The most common TEAEs of this category occurring in ≥ 2 subjects were AST increased, ALT increased, and Blood bilirubin increased. One subject met liver safety monitoring criteria (Blood bilirubin increased), which the Investigator assessed the event as unlikely related to seladelpar; however, the subject discontinued treatment after the event.
Risk groups or risk factors	Whilst the mechanism of potential hepatotoxicity with high doses of seladelpar in patients with PBC is unknown, it can be expected that the potential for drug-induced liver injury as reflected in increases in liver enzymes, including transaminases, may vary according to the stage of the underlying disease. Substages of cirrhosis are associated with increasing degrees of hepatic impairment (defined in seladelpar HI studies as CP-A, CP-B and CP-C) and potentially increased exposures to seladelpar.
Preventability	The SmPC states that dose dependent increases in serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) have been observed in patients receiving higher doses of seladelpar. The SmPC advises that monitoring of transaminase levels should be considered at initiation and while taking seladelpar. Consider temporary interruption of seladelpar treatment if liver tests worsen, or the patient develops signs and symptoms consistent with liver dysfunction. Consider permanent discontinuation if liver tests worsen again after restarting seladelpar.
Impact on the benefit-risk balance of the product	Findings suggestive of liver injury may require more frequent monitoring, cessation of treatment, and, in the most serious cases, hospitalization and supportive treatment. Liver function monitoring should be performed as per clinical practice. The benefit is considered to be positive in the indicated population with limited treatment options. The finding of elevated transaminases occurred at doses 5 times above the approved dose. Routine pharmacovigilance activities will further characterise the risk of transaminase elevation with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data. Advice on how to minimize the risk of transaminase elevation is disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive.
Public health impact	Minimal due to the rarity of the indication.

SVII.3.2. Presentation of the Missing Information

Table SVII.5. Missing Information

Missing Information	Evidence Source
Use in Pregnancy	Population in need of further characterization: In pregnant rabbits, the administration of 40 mg/kg/day (40.6-fold above the clinical AUC) was associated with reduced maternal and foetal body weights, but no foetal anomalies. In pregnant and lactating female rats, the administration of 100 mg/kg/day (145.2-fold above the clinical AUC) was associated with reduced maternal food consumption and body weight gain. The first filial (F1) generation offspring had reduced survival and body weight gain during the lactation period, with associated delays in developmental milestones at this dose. Although body weight decrements persisted during the post-weaning period, the rate of weight gain was comparable. No effects on postnatal development were seen at the next lowest dose of 20 mg/kg/day (15.2-fold above the clinical AUC). As per clinical study practice, pregnant subjects were excluded from clinical studies with seladelpar. There are therefore limited data on the use of seladelpar in pregnant women.
Long term safety	Due to the chronic nature of the condition, patients with PBC might require long term therapy with seladelpar and availability of data on safety of the long-term treatment over 2 years is limited. The primary evidence of the safety of seladelpar in PBC is provided from the phase 3, double-blind, randomised, placebo-controlled study CB8025-32048 (RESPONSE) that evaluated oral seladelpar 10 mg once daily versus placebo over 52 weeks (12 months), further supported with data from study CB8025-31735 (ENHANCE), with the primary analysis at 3 months. At the time of submission there was limited experience beyond 2 years of continuous use. While available data indicate safety remains consistent with extended exposure, including exposure beyond 2 years, this will continue to be reflected as missing information while additional data accrue for ongoing studies.
Use in PBC patients with moderate (Child Pugh B) hepatic impairment	The seladelpar clinical development program in PBC included primarily participants without cirrhosis and with compensated cirrhosis, nearly all Child Pugh A; seladelpar appeared overall safe and well tolerated in patients across the population studied. Child Pugh B patients with compensated cirrhosis are included in the ongoing PBC Study CB8025-41837 (AFFIRM), However, limited data is still available for this patient population. There is possibility that liver disease, including more advanced cirrhosis, may slow drug metabolism. As a result, drug exposure might be increased resulting in possible changes to the safety profile of seladelpar in this patient population. Two PK studies for seladelpar have been conducted with the main aim to evaluate pharmacokinetics and metabolism of seladelpar in participants with varying degrees of hepatic impairment (Study CB8025-11732 and Study CB8025-21838). In study CB8025-21838, close to 2-fold increases in exposures were seen in participants with CP-A with portal hypertension or with CP-B cirrhosis and slightly above 2-fold increases in exposures were seen in participants with CP-C cirrhosis compared to participants with CP-A

Missing Information	Evidence Source
	cirrhosis without PHT. No safety concerns related to seladelpar were identified, but data were available in a limited number of participants with repeated dosing of seladelpar ≤ 10 mg for 28 days. Use of seladelpar in PBC patients with moderate (CP-B) hepatic impairment may be of interest to healthcare providers given limited treatment options in this population and the possibility of benefit, hence it is considered missing information. In contrast, in patients with severe (Child Pugh C) hepatic impairment, treatment with seladelpar is not expected due to understanding by treating clinicians of low likelihood of a treatment benefit (rather, these patients may be evaluated for liver transplant). Based on small numbers of patients enrolled and potential for higher exposures in the setting of advancing hepatic impairment, no conclusions could be made on the safety of seladelpar treatment in patients with moderate (Child Pugh B) hepatic impairment. Therefore, use in PBC patients with moderate (Child Pugh B) hepatic impairment is proposed to be included as missing information.

PART II: MODULE SVIII—SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	Hepatotoxicity
Missing Information	Use in pregnancy
	Long term safety
	Use in PBC patients with moderate (Child Pugh B) hepatic impairment

PART III: PHARMACOVIGILANCE PLAN

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Drug Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

There are no specific adverse reaction follow-up questionnaires for any of the safety concerns.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2 Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study CB8025-31731-RE (Ongoing): ASSURE: An Open Label Long-Term Study to Evaluate the Safety and Tolerability of Seladelpar in Subjects with Primary Biliary Cholangitis (PBC).	
Rationale and Study Objectives	**Primary objective:** • To evaluate long term safety and tolerability of seladelpar **Secondary objectives:** • To evaluate the long-term efficacy of seladelpar • To evaluate the effect of seladelpar on patient-reported outcomes (pruritus) **Exploratory objectives:** • To evaluate the effect of seladelpar on liver histology, additional measures of quality of life (QoL), biomarkers of cholestasis, lipids and liver fibrosis • To evaluate plasma concentrations of seladelpar and its metabolites
Study Design	Open label, uncontrolled, international multicenter long-term interventional study.
Study Populations	The study includes subjects who participated in completed PBC study with seladelpar (CB8025-21629, CB8025-31735, CB8025-31731 and/ or CB8025-32048) or current PBC study CB8025-21838, and may include subjects from future PBC studies with seladelpar that allow rollover into CB8025-31731-RE.
Milestones	Interim study report: 13 Nov 2023 (data cut off 29 Jun 2023) Study completion: November 2028 Final study report: August 2029

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study and 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 or a marketing authorization under exceptional circumstances				
None				
Category 3—Required additional pharmacovigilance activities				
Study CB8025-31731-RE (ASSURE) An Open Label Long-Term Study to Evaluate the Safety and Tolerability of Seladelpar in Subjects with Primary Biliary Cholangitis (PBC) Ongoing	Primary objective: • To evaluate long term safety and tolerability of seladelpar Secondary objectives: • To evaluate the long-term efficacy of seladelpar • To evaluate the effect of seladelpar on patient-reported outcomes (pruritus) Exploratory objectives: • To evaluate the effect of seladelpar on liver histology, additional measures of quality of life (QoL), biomarkers of cholestasis, lipids and liver fibrosis • To evaluate plasma concentrations of seladelpar and its metabolites	• Hepatoxicity • Use in PBC patients with moderate (Child Pugh B) hepatic impairment • Long term safety	Interim study report	13 Nov 2023 (data cut off 29 Jun 2023)
			Study Completion	November 2028
			Final Study Report	August 2029

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1. Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study and Status	Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
CB8025-41837 (AFFIRM) A randomised, double-blind, placebo-controlled, study to evaluate the effect of seladelpar on clinical outcomes in patients with compensated cirrhosis and PBC Ongoing	To evaluate the effect of seladelpar compared to placebo on event-free survival (EFS). To evaluate the safety of seladelpar over 156 weeks of treatment compared with placebo. This study will address the safety concerns of: • Hepatotoxicity, • Use in PBC patients with moderate (Child Pugh B) hepatic impairment and • Long term safety	To evaluate the effect of seladelpar on clinical outcomes in patients with compensated cirrhosis and PBC	Final Protocol	12 Jan 2023
			Protocol submission to EMA	Q2 2025
			Study Completion	August 2030
			Final Clinical Study Report	February 2031

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

V.1 Routine Risk Minimization Measures

The routine risk minimization measure for Lyvdelzi in the EU comprise of the SmPC, the package leaflet (PL), and the legal status of the product. Lyvdelzi is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of PBC (SmPC Section 4.2). The routine risk minimization recommendations provided by the SmPC and PL are described further by safety concern in Table Part V.1. The legal status can be considered a general measure applicable to all individual safety concerns.

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Hepatotoxicity	**Routine risk communication:** SmPC section 4.4 PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4: Obtain baseline clinical and laboratory assessments at initiation of treatment with seladelpar and monitor thereafter according to routine clinical practice. Consider temporary interruption of seladelpar treatment if liver tests worsen, or the patient develops signs and symptoms consistent with liver dysfunction. Consider permanent discontinuation if liver tests worsen again after restarting seladelpar. Other routine risk minimization measures beyond the Product Information: **Medicine's legal status:** Prescription only medicine
Use in pregnancy	**Routine risk communication:** SmPC section 4.6 and 5.3 PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.2: As a precautionary measure, it is preferable to avoid the use of seladelpar during pregnancy Other routine risk minimization measures beyond the Product Information: **Medicine's legal status:** Prescription only medicine
Long term safety	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None

Safety Concern	Routine Risk Minimization Activities
	Other routine risk minimization measures beyond the Product Information: **Medicine's legal status:** Prescription only medicine
Use in PBC patients with moderate (Child Pugh B) hepatic impairment	**Routine risk communication:** SmPC Section 4.2 PL none **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.2: Consider discontinuing seladelpar if the patient progresses to moderate hepatic impairment. Use is not recommended in patients with severe hepatic impairment. Other routine risk minimization measures beyond the Product Information: **Medicine's legal status:** 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 Risk Minimization Measures

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None		
Important potential risk(s)		
Hepatotoxicity	**Routine risk minimisation measures:** SmPC section 4.4 PL section 2 Prescription-only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CB8025-31731-RE

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Use in pregnancy	**Routine risk minimisation measures:** SmPC section 4.6 SmPC section 5.3 PL section 2 Prescription-only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long term safety	**Routine risk minimisation measures:** SmPC none PL none Prescription-only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CB8025-31731-RE
Use in PBC patients with moderate (Child Pugh B) hepatic impairment	**Routine risk minimisation measures:** SmPC section 4.2 PL none Prescription-only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CB8025-31731-RE

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. Summary of risk management plan for Lyvdelzi

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

Lyvdelzi's summary of product characteristics (SmPC) and its product leaflet (PL) give essential information to health care professionals and patients on how Lyvdelzi should be used.

This summary of the RMP for Lyvdelzi 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 Lyvdelzi's RMP.

II. The Medicine and What Is It Used For

Lyvdelzi is authorized for primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA alone, or as monotherapy in adults unable to tolerate UDCA (see SmPC for the full indication). It contains seladelpar lysine as the active substance and it is given by oral route of administration.

Further information about the evaluation of Lyvdelzi benefits can be found in Lyvdelzi EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: link to the EPAR.

Risks Associated With the Medicine and Activities to Minimise or Further Characterize the Risks Important risks of Lyvdelzi, together with measures to minimise such risks and the proposed studies for learning more about Lyvdelzi's risks, are outlined below.

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

- Specific Information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and health care 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 public (eg, with or without prescription) can help to minimises 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 Periodic Safety Update Report (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 Lyvdelzi is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Lyvdelzi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken 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 Lyvdelzi. 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 (eg, on the long-term use of the medicine).

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	Hepatotoxicity
Missing Information	Use in pregnancy
	Long term safety
	Use in PBC patients with moderate (Child Pugh B) hepatic impairment

II.B. Summary of Important Risks

Lyvdelzi has been assigned the legal status of a medicine subject to medical prescription in the EU, whereby therapy should be initiated by a doctor experienced in the management of PBC (as described in Section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**None**
Important potential risk	**Hepatotoxicity**
Evidence for linking the risk to the medicine	**Non-clinical findings:** Minimal, reversible, hepatocellular necrosis was observed in male rats receiving the highest dose of 50 mg/kg/day in the 26-week study and male monkeys receiving ≥5 mg/kg/day for 52 weeks. **Clinical findings:** Seladelpar has been associated with transient dose dependent increases in serum transaminases (AST and ALT) levels greater than 3 times upper limit of normal (ULN) in subjects with PBC receiving doses of 50 and 200 mg/day (5- and 20-times the recommended 10 mg/day dose). Transaminase levels returned to pretreatment levels upon treatment discontinuation.
Risk factors and risk groups	The potential for drug-induced liver injury as reflected in increases in liver enzymes, including transaminases, may vary according to the stage of the underlying disease. Decreased hepatic function can lead to higher drug exposure increasing the risk of drug injury. Existing injury to the parenchyma and vascular system can increase the risk of injury.
Risk minimization measure(s)	**Routine risk minimization measures:** SmPC section 4.4 PL section 2 Prescription-only medicine **Additional risk minimization measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CB8025-31731-RE See Section II.C of this summary for an overview of the postauthorization development plan.
Missing information	**Use in pregnancy**
Risk minimization measure(s)	**Routine risk minimization measures:** SmPC section 4.6 SmPC section 5.3 PL section 2 Prescription-only medicine **Additional risk minimization measures:** None

Missing information	**Long term safety**
Risk minimization measure(s)	**Routine risk minimization measures:** SmPC none PL none Prescription-only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Study CB8025-31731-RE
Missing information	**Use in PBC patients with moderate (Child Pugh B) hepatic impairment**
Risk minimization measure(s)	**Routine risk minimization measures:** SmPC Section 4.2 PL none Prescription-only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Study CB8025-31731-RE

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

Table Part VI.3. Studies as Condition of the Marketing Authorization

Short Study Name	Purpose of the Study
CB8025-41837 **(AFFIRM)** A randomised, double-blind, placebo-controlled, study to evaluate the effect of seladelpar on clinical outcomes in patients with compensated cirrhosis and PBC	To evaluate the effect of seladelpar compared to placebo on event-free survival (EFS). To evaluate the safety of seladelpar over 156 weeks of treatment compared with placebo. This study will address the safety concerns of: • Hepatotoxicity, • Use in PBC patients with moderate (Child Pugh B) hepatic impairment • Long term safety

II.C.2. Other Studies in Postauthorization Development Plan

Table Part VI.4. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
CB8025-31731-RE (ASSURE) An Open Label Long-Term Study to Evaluate the Safety and Tolerability of Seladelpar in Subjects with Primary Biliary Cholangitis (PBC).	Primary objective: • To evaluate long term safety and tolerability of seladelpar

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed and Ongoing Studies in the Pharmacovigilance Plan

Study CB8025-31731-RE (ASSURE)

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

None

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

Study CB8025-41837 (AFFIRM)

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

None

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

Referenced material (Refer to REFERENCES)

Annex 8. Summary of Changes to the Risk Management Plan Over Time

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ELECTRONIC SIGNATURES

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Rainer Heissing	QPPV eSigned	04-Jun-2025 14:27:08
[redacted]	Global Development Lead (GDL) eSigned	04-Jun-2025 14:51:04
[redacted]	Patient Safety eSigned	04-Jun-2025 15:31:27