Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Livdelzi

Active ingredient: Seladelpar

Sponsor: Gilead Sciences Pty Ltd

May 2026

OFFICIAL

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMA	Anti-Mitochondrial Antibodies
ANA	Anti-Nuclear Antibodies
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
BMI	Body Mass Index
C4	7α-Hydroxy-4-Cholesten-3-One
CCDS	Company Core Data Sheet
CERC	Critical Events Review Committee
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CK	Creatine Kinase
Cmax	Maximum Plasma Concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CP	Child-Pugh Classification
CPRC	Clinico-Pathological Review Committee
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DSIC	Drug Substance in Capsule
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
eGFR	Estimated Glomerular Filtration Rate

Abbreviation	Meaning
EMA	European Medicines Agency
EMEA	Europe, the Middle East, and Africa
EOT	End of Treatment
E-R	Exposure-Response Analysis
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FMQ	FDA Medical Query
FXR	Farnesoid X Receptor
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HDL	High-Density Lipoprotein
HI	Hepatic Impairment
HoFH	Homozygous Familial Hypercholesterolemia
ICH	International Council for Harmonisation
IL-31	Interleukin-31
ITT	Intent-to-Treat
LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal
LS	Least Squares
MAA	Marketing Authorisation Application
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	Modified Intent-to-Treat
MMRM	Mixed-Effect Model Repeated Measure
MRL	Medpace Reference Laboratories
MSPN	Moderate-to-Severe Pruritus NRS
NASH	Non-alcoholic Steatohepatitis
NCA	National Competent Authority
NCI	National Cancer Institute
NDA	New Drug Application
NPC1L1	Niemann-Pick C1-Like 1 Protein

Abbreviation	Meaning
NRS	Numerical Rating Score
NCA	National Competent Authority
NCI	National Cancer Institute
NDA	New Drug Application
NPC1L1	Niemann-Pick C1-Like 1 Protein
NRS	Numerical Rating Score
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCA	Obeticholic Acid
PBC	Primary Biliary Cholangitis
PBC-40	Primary Biliary Cholangitis-40 Quality of Life Questionnaire
PBPK	Physiologically Based Pharmacokinetic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P-Glycoprotein
PHT	Portal Hypertension
PK	Pharmacokinetic(s)
popPK	Population Pharmacokinetics
PPARδ	Peroxisome Proliferator-Activated Receptor δ
PPI	Proton Pump Inhibitors
PR	Interval of Atrial Depolarisation
PRC	Pathology Review Committee
PRIME	Priority Medicines
PRS	Pathology Review Subcommittee
PT	Preferred Term
QD	Quaque Die, Once a Day
QoL	Quality of Life
QRS	Interval of Ventricular Depolarisation
QT	Interval of Ventricular Depolarisation and Ventricular Repolarisation
QTcF	Corrected QT Interval Calculated by Fridericia's Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation	Meaning
SE	Standard Error
SHRC	Seladelpar Hepatotoxicity Review Committee
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
Tmax	Time to Reach the Maximum Plasma Concentration
TQT	Thorough QT/QTc
UDCA	Ursodeoxycholic Acid
ULN	Upper Limit of Normal
US	United States
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
Vc	Apparent Volume of Distribution

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Livdelzi seladelpar 10 mg capsule bottle
Active ingredient:	Seladelpar lysine
Decision:	Approved
Date of decision:	22 January 2026
Date of entry into ARTG:	28 January 2026
ARTG number:	473285
▼*Black Triangle Scheme for the current submission:*	Yes
Sponsor's name and address:	Gilead Sciences Pty Ltd
Dose form:	Capsule
Strength:	10mg
Container:	Bottle
Pack size:	30 capsules
Approved therapeutic use for the current submission:	Livdelzi 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.
Route of administration:	Oral
Dosage:	The recommended dosage of Livdelzi is 10 mg taken orally once daily with or without food. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	Category B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during

pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Gilead Sciences Pty Ltd (the sponsor) to register Livdelzi (seladelpar) 10mg capsules for the following proposed indication:[1]

> *Seladelpar is indicated for the treatment of primary biliary cholangitis (PBC), including pruritus, in adults in combination with ursodeoxycholic Acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.*

The recommended dose of Seladelpar is 10 mg once daily.

Disease or condition – Primary biliary cholangitis (PBC)

PBC is a serious, rare, slowly progressive, and potentially life-limiting liver disease characterised by immune-mediated degeneration of bile ducts, impaired bile flow (cholestasis) and accumulation of toxic bile acids. Although the exact aetiology of PBC is unknown, immunological dysfunction triggered by environmental factors (such as cigarette smoking, toxin exposure, and infectious agents) may render autoimmunity against the interlobular bile ducts in genetically predisposed hosts (You H, 2022).

PBC typically affects middle-aged women, commonly presents with fatigue and pruritus, or with an asymptomatic elevation of serum alkaline phosphatase (ALP)/glutamyl transpeptidase (GGT). The pathological features are progressive, non-suppurative, destructive intrahepatic cholangitis, leading to fibrosis and eventually cirrhosis. Antimitochondrial antibodies (AMAs), especially the M2 subtype (AMA-M2), are highly sensitive and specific for PBC in clinical settings. There is strong evidence indicating that diagnosis of PBC can be established when meeting two or more of the following three criteria:

1. Biochemical evidence of cholestasis based mainly on the elevation of ALP and GGT with the exclusion of extrahepatic biliary obstruction by imaging studies.
2. Presence of AMA or other PBC-specific ANAs including anti-sp100 or anti-gp210.
3. Histologic evidence of non-suppurative destructive cholangitis mainly affecting the interlobular bile ducts (You H, 2022).

Current treatment options

It is recommended that oral UDCA (13 ~ 15 mg/kg/day) should be standard therapy for all PBC patients. However, about 30–40% of PBC patients show insufficient biochemical responses to UDCA and remain at risk for disease progression to advanced stages, including cirrhosis.

Obeticholic acid (OCA) and elafibranor (IQIRVO) are both registered in Australia for 'the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA'.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

Clinical rationale

As per the sponsor's submission:

Seladelpar is a novel, potent, and selective PPARδ agonist (i.e., a delpar) that targets multiple cell types in the liver, leading to anticholestatic, anti-inflammatory, antipruritic, and antifibrotic effects in animal and human studies. Selectivity of seladelpar for PPARδ over PPARα is approximately 630-fold in humans with no evident activation of PPARγ.

The rationale for assessing seladelpar as a treatment for PBC includes its impact on bile acid synthesis via both FGF21 and NPC1L1, anti-inflammatory and antifibrotic effects in the liver as well as its anti-pruritic effects.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity (NCE) for Australian regulatory purposes.

International regulatory status

The current international regulatory status of seladelpar is summarised in Table 1.

Most notably, seladelpar has conditional marketing authorisation in the EU and has accelerated approval in the US. Seladelpar is also approved in the United Kingdom.

Table 1: International regulatory status at the time this submission was assessed

Region	Submission date	Approved	Indications (approved or requested)
USA	14 December 2024	14 August 2024	Livdelzi 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, or as monotherapy in patients unable to tolerate UDCA.
European Union	12 February 2024	20 February 2025 (Conditional Marketing Authorisation)	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.

Region	Submission date	Approved	Indications (approved or requested)
United Kingdom (England, Wales, Scotland, Northern Island)	26 January 2024	16 January 2025	Livdelzi is indicated for the treatment of primary biliary cholangitis (PBC), including pruritus, in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA, or as monotherapy in those unable to tolerate UDCA.
Canada	13 January 2025	16 October 2025	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 adults unable to tolerate UDCA.
Israel	1 April 2025	8 December 2025	Livdelzi 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.
Switzerland	23 January 2025	9 December 2025	Lyvdelzi is indicated for the treatment of primary biliary cholangitis (PBC), in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.

No applications for this product have been rejected, withdrawn or repeatedly deferred on the grounds of safety or efficacy.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for assessment of this submission

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2025
Evaluation completed (End of round 2)	22 October 2025
Advisory committee meeting	4-5 December 2025
Registration decision (Outcome)	19 December 2025
Registration in the ARTG completed	28 January 2026
Number of working days from submission dossier acceptance to registration decision*	125 days

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Quality evaluation summary

Seladelpar is a single *R*-configuration enantiomer and is present as a lysine dihydrate salt. The drug substance is produced by chemical synthesis. It is manufactured as the crystalline Form A polymorph, the only identified polymorph. The drug substance exists as a variable hydrate, with no change in the crystal form between 1% and 80% RH.

Risk evaluations on the potential presence of nitrosamines and elemental impurities were performed. No significant risk was identified.

The long-term and accelerated stability studies support the proposed retest period of 60 months when stored at controlled room temperature (20 to 25°C).

The drug substance is not photolabile, and the product does not require special protection from light exposure.

The data supports a shelf-life of 48 months when stored below 25°C.

The supported in-use shelf life is 30 days after the first opening of the bottle.

The product used in the Phase 3 clinical studies differed to the product proposed for registration (i.e. neat drug substance in capsules versus the proposed capsule formulation). The formulation differences were adequately bridged by a bioequivalence study. The 90% CIs for GLSM ratio between the products were within the range 80.00-125.00% for C_{max} and AUC, supporting the conclusion that the formulations were bioequivalent. The results for the study suggest that the rate and extent of absorption is not significantly affected by the formulation differences.

Recommendation from the quality evaluator

The Product Information and labelling is considered acceptable from a pharmaceutical quality perspective. There are no objections to registration from a quality perspective.

Nonclinical evaluation summary

Gilead Sciences Pty Ltd has applied to register a new chemical entity, seladelpar (Livdelzi), a PPARδ receptor agonist for the treatment of primary biliary cholangitis (PBC), including pruritus, in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA. The proposed dose is one tablet (10 mg) per day. No maximum treatment period is specified.

The submitted Module 4 dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceuticals (ICH M3(R2)). The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were GLP compliant. No major deficiencies were identified.

In vitro, seladelpar bound PPARδ with nanomolar affinity, activated it with an EC_{50} value within expected clinical plasma concentrations, and increased expression of PPARδ target genes. The major circulating metabolites, M1 (sulfoxide metabolite), M2 (O-desethyl metabolite) and M3 (O-desethyl sulfoxide metabolite), do not contribute the pharmacological activity of seladelpar.

In vivo, oral/dietary administration of seladelpar to mice decreased hepatic bile acid synthesis and intestinal cholesterol absorption, and reduced liver fibrosis in an experimental model. These findings support the use of seladelpar for the treatment of primary biliary cholangitis in the proposed population.

Seladelpar activated PPARs α and γ, with ~600-fold less potency than PPARδ. PPARα activation contributed to several effects seen in general toxicity and carcinogenicity studies; however, PPARα activation is not expected in humans. Seladelpar also inhibited the Cl- channel modulatory site of the GABAA/benzodiazepine receptor complex at micromolar concentrations not considered clinically relevant.

Safety pharmacology studies assessed effects on the cardiovascular, respiratory, and central nervous systems. No adverse effects were seen on CNS function in rats, respiratory function in dogs, or cardiovascular function in dogs or monkeys. No significant inhibition of hERG K+ channel tail current was observed at clinically relevant concentrations. Seladelpar is not predicted to prolong the QT interval in patients.

Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Seladelpar was readily and rapidly absorbed with a similar T_{max} in all species. Half-life values were moderate in mice, rats and humans but longer in dogs and monkeys. Plasma protein binding of seladelpar and its metabolites was moderate to very high in all animal species and humans. Tissue distribution of seladelpar was wide but penetration into brain and spinal cord was limited and no binding to melanin evident. Metabolism of seladelpar was chiefly mediated by CYP2C8, CYP2C9 and CYP3A4, with an additional minor contribution by CYP1A2. The main human metabolites (M1, M2 and M3) were significant metabolites in animals. Drug-related material was excreted via urine and faeces with urine as the predominant route of excretion in humans, while faeces predominated in rats.

Based on *in vitro* and clinical studies, inhibitors of CYP2C8, CYP2C9 and CYP3A4 could increase exposure to seladelpar and M1. Seladelpar was a substrate of BCRP, P-gp and OAT3; inhibitors of BCRP and OAT3 therefore have potential to increase seladelpar exposure. Although seladelpar

inhibited BCRP *in vitro*, clinical studies using rosuvastatin (a BCRP and OATP substrate) suggest that seladelpar is unlikely to impact BCPR substrates in patients.

Seladelpar had a moderate order of acute oral toxicity in mice and rats.

Repeat-dose toxicity studies by the oral route were conducted in mice (up to 3 months), rats (up to 6 months), dogs (up to 4 weeks) and monkeys (up to 12 months). Very high multiples of the clinical exposure were achieved for seladelpar and metabolites M1, M2 and M3 in all species, except for M2 in monkeys where exposure was moderate. Major findings comprised changes in the liver (increases in liver weight, hepatocellular hypertrophy, bile duct hyperplasia and hepatocellular necrosis), skeletal and cardiac muscle (myofiber and myocardial degeneration), GI tract (epithelial hyperkeratosis), kidney (increased weight with (at high doses in rats) tubular epithelial hyperplasia and chronic progressive nephropathy) and male reproductive organs in dogs (testicular interstitial cell and prostate atrophy).

Seladelpar and its metabolites were not genotoxic in the standard battery of tests. In 2-year rodent carcinogenicity studies, seladelpar-related findings in mice included an increased incidence of hepatocellular adenoma and carcinoma in males and combined hepatocellular adenoma and carcinoma in both sexes at subclinical doses. Treatment-related neoplastic findings in rats included an increased incidence of squamous cell carcinoma of the non-glandular stomach in males and an increased incidence of benign testicular interstitial cell tumours at high clinical exposures. All neoplastic findings in rats and mice were considered class and species specific and therefore not relevant to humans.

Male and female fertility were unaffected by seladelpar in rats, and no adverse effects on embryofetal development were observed. In rabbits, fetal body weight was reduced in the context of maternotoxicity. No fetal malformations occurred; a dose-related increase in distended stomach (fetal variation) was observed. Reductions in fetal body weight during lactation, with reduced pup survival and slight developmental delays, were observed in a pre/postnatal development study in rats.

Seladelpar is not expected to have phototoxic potential upon exposure to visible/UV light after repeat dosing. Seladelpar was a mild eye irritant in *in vitro* studies and did not provoke a delayed hypersensitivity response in mice.

All impurities in the drug substance and product are metabolites of seladelpar present in both humans and animals and are considered qualified.

Recommendation from the non-clinical evaluator

The nonclinical dossier contained no critical deficiencies.

Primary pharmacology studies, showing activation of PPARδ *in vitro* and decreased hepatic bile acid synthesis, reduced intestinal cholesterol absorption, and reduced liver fibrosis *in vivo* offer support for the proposed use of the drug in the treatment of PBC.

No clinically relevant hazards were identified from secondary and safety pharmacology studies.

Liver, skeletal and cardiac muscle, GI tract, kidney and male reproductive organs were identified as major targets for toxicity in repeat-dose studies. Toxicity was largely related to off-target activation of PPARα, was species-specific, or occurred at very high multiples of the clinical exposure. Since seladelpar is not expected to activate PPARα in humans, effects on these organ systems are considered unlikely to occur in patients.

There are no nonclinical objections to the registration of Livdelzi for the proposed indication.

Clinical evaluation summary

Summary of clinical studies

The clinical dossier included the following pivotal and supportive studies.

Pivotal study - CB8025-32048 (RESPONSE)

A single pivotal placebo-controlled, randomised, Phase III study to evaluate the efficacy and safety of seladelpar in patients with PBC and inadequate response to or intolerance to UDCA.

Supportive studies

1. Study CB8025-31735 (ENHANCE) was a phase III study in subjects with PBC having a design similar to the pivotal study. This study was terminated early.
2. Study CB8025-31731 was a phase III, open-label, long-term, study of seladelpar that enrolled subjects who completed study CB8025-21629 or CB8025-31735.
3. Study CB8025-31731-RE (ASSURE) is an ongoing, phase III, open-label, uncontrolled, multicentre study of seladelpar designed to evaluate the long-term safety, tolerability, and efficacy, and effect on patient-reported outcomes (pruritus) in subjects with PBC.
4. Study CB8025-21629 was a Phase II, open-label, 8-week dose-ranging (2, 5, and 10 mg once daily) study of seladelpar with a 44-week extension period.
5. Study CB8025-21528 was a Phase II, placebo-controlled, dose-ranging study of seladelpar (50mg and 200mg).

Efficacy evaluation

The clinical evaluator provided the following recommendation:

> *It is recommended that approval can be granted for slightly modified wording of proposed indication as follows: 'Seladelpar is indicated for the treatment of primary biliary cholangitis (PBC), in adults in combination with ursodeoxycholic Acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.'*

Pharmacokinetics

There was no evidence of change in exposure (AUC and Cmax) to seladelpar following oral administration as a capsule compared with the solution formulation in healthy male subjects. The relative bioavailability (capsule/solution) based on the geometric mean ratio of 1.06 for both AUC0-24 and AUC0-∞.

Seladelpar 10 mg was rapidly absorbed after a single oral dose, with a median Tmax of 1.5 hours (Study CB8025-11734). No significant accumulation was observed after multiple daily dosing, and steady state was achieved from Day 4 onwards after daily dosing.

Seladelpar exposure increased with increasing single doses of seladelpar from 1 to 360 mg. Increases in exposure were approximately dose proportional through the 15 mg dose, after which the increase in Cmax was larger than dose proportional.

Seladelpar and the M2 metabolite were found to be extensively bound (≥ 99.4%) to human plasma proteins in vitro (Module 2.6.4). In patients with PBC, the apparent volume of distribution at steady state of seladelpar at 10 mg was 110.3 L.

After oral administration, seladelpar was extensively metabolised and rapidly eliminated in urine in the form of metabolites. Urinary excretion was the major route of elimination for total radioactivity, with observed mean recovery of total radioactivity in urine of 73.4%. Urinary excretion of seladelpar as metabolites M1, M2, and M3 was greater than the parent drug, representing 8.34%, 1.17%, and 27.5% of the dose, respectively.

The metabolites M1, M2, and M3 were slowly produced and eliminated compared with seladelpar; the median Tmax was 10, 4 and 4 hours for metabolites M1, M2 and M3, respectively.

Effects of age, sex, weight, renal impairment, and hepatic impairment on seladelpar exposure were assessed as a covariate in the popPK analysis. There was no statistically significant effect of age, sex, or renal function (measured by eGFR) on seladelpar clearance, as the 95% CIs of the estimated effects included the null value. There was a trend of increasing clearance with increasing weight. The magnitude of the weight effect was considered within the range of between-subject variability and is therefore unlikely to be clinically meaningful.

The Phase I study **CB8025-11732,** evaluated the effects of hepatic impairment (HI) on PKs of seladelpar and its metabolites (M1, M2 and M3) in 32 subjects. Exposure to seladelpar and metabolites was generally similar in subjects with mild HI compared to normal subjects. The safety and efficacy of seladelpar in subjects with PBC with moderate to severe HI (Child-Pugh B or C) has not been established and no dosage recommendation can be given for subjects with Child-Pugh B or C hepatic impairment.

There was no meaningful increase in seladelpar plasma exposure following single oral dose of 10mg capsule (proposed formulation) with worsening renal function. An increase of 59% in seladelpar AUC was observed in the moderate renal impairment group with no increase in Cmax.

To further evaluate the plasma PK of seladelpar and to evaluate the impact of covariates of interest and subject variability, popPK (Report CYMA-PMX-SELADELPAR-4391-PPK- 202408), E-R (Report CYMA-PMX-SELADELPAR-4391-ER-20241031), and PBPK (Report CYMA-PBPK-SEL-1C-20231113) analyses were conducted. The main findings were: Typical PBC patient estimated clearances were 12.0 L/h for seladelpar and 4.44 L/h for M2, with between-subject variabilities of 38% and 47%, respectively. Seladelpar administration with food reduced seladelpar Cmax by 25% (15% for M2) but did not affect steady-state AUC significantly for either seladelpar or M2.

Pharmacodynamics

Across PBC clinical studies, rapid and consistent reductions in ALP were observed with seladelpar. Onset of ALP reductions have been demonstrated as early as Week 2 in study CB8025-21528, Week 1 in CB8025-21629, and Week 4 (the first timepoint assessed) in phase III studies CB8025-32048, CB8025-31735, CB8025-31731, and CB8025-31731-RE. ALP reduction in the phase III studies were sustained through 12 months and up to 24 months.

The reduction of C4 with other markers of cholestasis, including ALP and GGT suggests that seladelpar acts to improve cholestasis by reducing hepatocellular bile acid pools.

The effects of seladelpar on serum levels of FGF21 in study CB8025-32048 support FGF21 as a pharmacodynamic marker of the hepatocellular engagement of PPARδ by seladelpar in PBC subjects.

The effects of seladelpar on IL-31 levels in study CB8025-32048 support IL-31 as a pharmacodynamic marker of seladelpar effect on pruritus in PBC subjects.

Concentration regression analysis showed no effect of seladelpar concentration on the placebo-adjusted change of QTcF from baseline and seladelpar was not associated with significant QT

prolongation when administered in single-doses up to 200 mg. Assay sensitivity using moxifloxacin 400 mg was confirmed.

Changes in lipids (total cholesterol, LDL-C, and triglycerides) have been measured in PBC clinical studies with seladelpar and consistent reductions in total cholesterol, LDL-C, and triglycerides levels being observed (with no change in HDL-C levels).

Dosage selection for the pivotal studies

CB8025-21528 was a Phase II, 12-week, double-blind, randomised, placebo-controlled study to evaluate the effects of two doses of MBX-8025 (seladelpar 50mg and 200mg) in subjects with PBC and an inadequate response to UDCA.

This study demonstrated rapid and consistent decreases in ALP with both seladelpar doses (while subjects on placebo remained stable). The reductions in ALP in the MBX-8025 groups were also associated with decreases in the other cholestasis enzymes, GGT and 5'nucleotidase. Three subjects (1 on 50mg and 2 on 200mg seladelpar) developed grade 3 ALT elevations that were judged to be study medication related or possibly study medication related. The ALT elevations were dose-related, onset was rapid (noted after 2 weeks of treatment, the first evaluation time point), subjects were asymptomatic and there were no concurrent elevations in total bilirubin. The elevations were fully and quickly reversible upon treatment discontinuation (after 2 to 4 weeks). Furthermore, the 200mg dose was also associated with muscle pain associated with elevation in creatine kinase (peak was 4062 U/L; ULS is <170U/L). The event was diagnosed as a myopathy and considered to be possibly drug related.

In the Phase II study **CB8025-21629** dose-dependent improvements in markers of cholestasis, as well as metabolic markers (e.g., decrease in triglycerides and LDL-C) were observed following dosing with seladelpar 2, 5, and 10 mg doses. By Week 52, 10 of 11 subjects receiving seladelpar 2 mg up-titrated to 5 or 10 mg, and 30 of 53 subjects receiving seladelpar 5 mg up-titrated to 10 mg to improve clinical response.

The Phase III, 52-week, randomised, placebo-controlled study **CB8025-31735** evaluated the efficacy and safety of two seladelpar dose regimens (5mg/day titrated to 10mg/day and 10mg/day) in 265 subjects with PBC an inadequate response to or an intolerance to ursodeoxycholic acid (UDCA). Although the study and all its primary and key secondary endpoints were planned for 12 months, it was terminated early. However, results from this study contributed to selection of the final dose of 10mg/day. Both the 5 mg and 10 mg doses demonstrated efficacy, but the seladelpar 10 mg dose (N = 55) demonstrated superior efficacy in the composite endpoint (ALP < 1.67× ULN, ALP decrease of ≥ 15%, and total bilirubin ≤ ULN; 78.2% versus 57.1%) ($p<0.05$) with comparable safety compared to seladelpar 5 mg (N = 56) The proposed 10 mg dose was also superior to 5 mg ($p<0.01$) in normalising ALP (27.3% versus 5.4%), and in subjects with baseline NRS ≥ 4, seladelpar 10 mg showed improvement in pruritus (least square mean decrease in NRS of 3.15 versus 1.64 in placebo, $p<0.03$), whereas the seladelpar 5 mg effect was not statistically significant. Adverse events were reported in 74% 63%, and 65% of subjects receiving placebo, seladelpar 5 mg, and seladelpar 10 mg, respectively**.**

The pivotal Phase III study **CB8025-32048** was conducted using only the proposed dose of 10mg seladelpar once daily.

Pivotal study

Study CB8025-32048 (RESPONSE)

This was a Phase III, international. multicentre, randomised, double-blind, placebo-controlled, parallel-arm study to evaluate the efficacy and safety of Seladelpar in patients with PBC and an inadequate response to or an intolerance to UDCA.

The primary objectives were to evaluate:

- the treatment effect of seladelpar on composite biochemical improvement in cholestasis markers based on alkaline phosphatase (ALP) and total bilirubin at 12 months of treatment compared with placebo
- the safety of seladelpar over 12 months of treatment compared with placebo.

The key secondary objectives were to evaluate:

- the effect of seladelpar on the normalisation of ALP values at 12 months of treatment compared with placebo
- the effect of seladelpar on pruritus at 6 months of treatment compared with placebo in subjects with baseline moderate to severe pruritus.

The other secondary objectives were to evaluate:

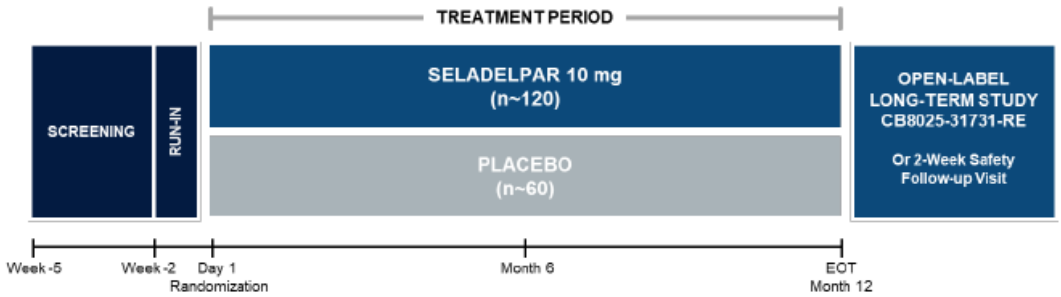
- the effect of seladelpar on quality of life (QoL)
- the effect of seladelpar on PBC-associated clinical outcomes.

The exploratory objectives were to evaluate:

- the effect of seladelpar on liver histology, additional measures of QoL, biomarkers of cholestasis and inflammation, lipids and auto-antibody profiles, bile acid synthesis, liver fibrosis and liver injury
- the plasma concentrations of seladelpar and metabolites.

The study design is summarised in **Figure 1** below.

Figure 1. CB8025-32048: Study design



Abbreviation: EOT = End-of-Treatment
Study drug was an add-on to UDCA for subjects with an inadequate response to UDCA in the prior 12 months or as monotherapy in subjects intolerant to UDCA.

On Day 1, subjects were randomly assigned in a 2:1 ratio to receive daily seladelpar 10 mg or placebo. Randomization was stratified by ALP level (< 350 U/L vs ≥ 350 U/L) and the presence of clinically important pruritus (Pruritus NRS < 4 vs NRS ≥ 4) to ensure even distribution across treatment arms. Subjects were considered formally enrolled in the study at the time of randomization.

The total duration of participation in the study for each subject was up to ~14 months. The Screening Period was up to 3 weeks, the Run-in Period was up to 2 weeks, and the Treatment Period was up to 12 months. During the Treatment Period, subjects visited the clinic every 3 months except for the first on-treatment visit, which was performed 1 month after the initiation of the study drug.

After completion of the Treatment Period, subjects were invited to enrol in an open-label, long-term study (CB8025-31731-RE) where each subject was to be administered seladelpar (and subjects previously randomised on placebo were to initiate seladelpar treatment). Subjects who declined participation in this long-term study had a Safety Follow-up Visit performed 2 weeks (14 days +3) after the last dose of the study drug.

The histological status of subject's liver was evaluated before and after treatment. All subjects were encouraged to have a liver biopsy during the Screening Period (unless a historical biopsy meeting quality standard was available) to evaluate PBC stage and histopathology changes from baseline to 1 year following treatment. The follow-up liver biopsy was performed only in subjects with a baseline liver biopsy at Month 12 or at ET if the subjects withdrew from the study early, provided they had received at least 6 months of treatment.

The study was conducted in 193 PBC subjects across 90 sites in 24 countries. It was conducted from 21 April 2021 to 11 August 2023.

The main criteria for inclusion were:

1. male or female aged 18 to 75 years
2. confirmed PBC as defined by having any 2 of the following 3 diagnostic criteria:
    a. history of ALP above 1.0× ULN for at least 6 months
    b. positive AMA titres (> 1:40 on immunofluorescence or M2 positive by ELISA) or positive PBC-specific ANAs
    c. documented liver biopsy results consistent with PBC
3. UDCA for the past 12 months (stable dose for > 3 months prior to screening) OR intolerant to UDCA (last dose of UDCA > 3 months prior to screening)
4. laboratory parameters measured by the Central Laboratory at Screening:
    a. ALP ≥ 1.67× ULN
    b. AST ≤ 3× ULN
    c. ALT ≤ 3× ULN
    d. Total bilirubin ≤ 2× ULN
    e. eGFR > 45 mL/min/1.73m2 (calculated by the Modification of Diet in Renal Disease Study equation)
    f. INR < 1.1× ULN (For subjects on anticoagulation therapy, INR must have been maintained in the range required for prophylaxis for their specific disease
    g. Platelet count ≥ 100×103/μL.

The main exclusion criteria were:

1. advanced PBC as defined by the Rotterdam criteria (albumin below the LLN and total bilirubin above 1.0× ULN)

a. presence of clinically important hepatic decompensation, including-

b. history of liver transplantation, current placement on liver transplantation list, or current MELD score ≥ 12.[2]

c. complications of PHT, including known oesophageal varices, history of variceal bleeds or related interventions (e.g., transjugular intrahepatic portosystemic shunt placement), ascites, and hepatic encephalopathy

2. cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma, or hepatorenal syndrome

3. treatment with OCA and fibrates (e.g., bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, and saroglitazar) 6 weeks prior to screening

4. treatment with antipruritic drugs (e.g., cholestyramine, naltrexone, rifampicin, sertraline, or any experimental approach) must have been on a stable dose within 1 month prior to screening

5. treatment with colchicine, methotrexate, azathioprine, or long-term systemic corticosteroids (> 2 weeks) during 2 months prior to screening

6. other chronic liver diseases, known history of HIV, malignancy.

Study treatments

Enrolled subjects were randomized into the study to receive seladelpar 10mg once daily versus placebo in a 2:1 ratio. The study drug (seladelpar or placebo) was administered orally, once daily, for a duration of up to 12 months. Subjects were instructed to take 1 capsule every Day, at approximately the same time. Subjects who met specific safety monitoring criteria or had tolerability issues could have a dose down-titration. Subjects who were initially assigned to 10 mg seladelpar were down titrated to 5 mg seladelpar in a blinded manner. Subjects initially assigned to placebo had a blinded down titration and remained in the placebo arm. UDCA was taken as a background therapy as part of participation in the study.

The primary endpoints were:

1. proportion of subjects who were considered responders at 12 months based on the following composite endpoint of ALP and total bilirubin at 12 months requiring

   a. ALP < 1.67× ULN

   b. ≥ 15% decrease in ALP

   c. Total bilirubin ≤ 1.0× ULN

2. assessment of treatment-emergent AEs (TEAEs) (National Cancer Institute [NCI] Common.

3. Terminology Criteria for Adverse Events [CTCAE] Version 5.0), biochemistry and haematology.

The key secondary endpoints were:

4. proportion of subjects with ALP ≤ 1.0× ULN at 12 months (e.g., normalisation)

[2] For subjects on anticoagulation medication, evaluation of the baseline INR, in concert with their current dose adjustments of their anticoagulant medication, was taken into account when calculating the MELD score. This was done in consultation with the Medical Monitor.

5. change from baseline in weekly averaged Pruritus NRS in subjects with baseline NRS ≥ 4 at 6 months.

Subjects were randomized in a blinded manner to receive seladelpar 10 mg or placebo in a 2:1 ratio. In addition, randomisation was stratified by ALP level (< 350 U/L vs ≥ 350 U/L) and by the presence of clinically important pruritus (Pruritus NRS < 4 vs NRS ≥ 4).

A sample size of 180 randomized subjects who received study drug provided > 90% power to detect a difference between the 10 mg seladelpar arm and the placebo arm (with the use of a 2-sided test of equality of binomial proportions based on Fisher's exact test at the 0.05 level of significance). This was based on the assumption of response rates of 20% and 55% for the primary efficacy endpoint (composite biochemical response of ALP and total bilirubin) in the placebo and seladelpar treatment groups, respectively.

For the key secondary efficacy endpoint of normalisation of ALP levels, the response rate for placebo and seladelpar was estimated to be 2.5% and 25.5% respectively. A sample size of 180 was calculated based on 2-sided Fisher's exact test with alpha at 0.05 to provide >90% power to detect a difference between Seladelpar and placebo group. For the key secondary efficacy endpoint of change from baseline in weekly averaged Pruritus NRS at Month 6, a sample size of 48 subjects was calculation based on a 2-sample 2-sided t-test with a significance level of 0.05 and a common standard deviation estimated at 2. Under these assumptions, the test would provide >80% power to detect a treatment difference of ≥2 between 10-mg seladelpar and placebo groups.

Participant flow

Of the 360 subjects who were screened, a total of 193 subjects were randomised to receive study treatment (128 and 65 in seladelpar and placebo arms, respectively). The 165 screen failures were mostly due to not meeting laboratory parameter thresholds for ALP, ALT, AST, eGFR, or total bilirubin.

Overall, 175 (90.7%) of the subjects completed the study. The percentage of subjects who did not complete study treatment was lower in the seladelpar arm (seladelpar vs placebo: 7.8% vs 12.3%). The most common reasons for early treatment discontinuation in both arms were adverse events (3.1% vs 6.1%) and withdrawal of informed consent (3.1% vs 3.1%).

Baseline data

The mean age of subjects was 56.7 years with a range of 28 to 75 years old with majority being female (94.8%), white (88.1%), non-Hispanic or Latino (69.9%) and from EMEA (39.4%), North America (32.6%) and Latin America (22.3%).

Overall, baseline demographics were well-balanced between the seladelpar and placebo treatment arms with a few exceptions [seladelpar arm had more subjects from North America (39.1% vs 20%) and were non-Hispanic/Latino (75.8% vs 58.6%)]. Most subjects (93.8%) were on UDCA treatment at baseline, while 12 subjects (6.2%) were intolerant to UDCA (6.3% vs 6.2%). The mean baseline laboratory values, including ALP and total bilirubin (categorical variables in the primary composite biochemical response endpoint), were generally similar between treatment arms.

Results for the primary efficacy outcome

Seladelpar treatment led to a significantly higher percentage of subjects achieving the primary efficacy endpoint of composite biochemical response at Month 12 (61.7% vs 20%; risk difference=41.7%; 95% CI: 27.7, 53.4; p < 0.0001).

The improvement was consistent for the ALP < 1.67× ULN component of the composite biochemical response endpoint (65.6% vs 26.2%) and percentage of subjects with a decrease from baseline of ≥ 15% in ALP levels (83.6% vs 32.3%). The difference between seladelpar and placebo was much smaller for percentage of subjects with total bilirubin ≤ 1.0× ULN (81.3% vs 76.9%) (Table 2).

Table 2. Analysis of the Composite Biochemical Response Endpoint at Month 12 (ITT Analysis Set)

	Placebo (N = 65)	Seladelpar 10 mg (N = 128)
Subjects Who Achieved Response at Month 12[a,b], n (%) (Wald 95% CI for Response Rate)	13 (20.0) (10.3, 29.7)	79 (61.7) (53.3, 70.1)
Risk Difference (Miettinen-Nurminen 95% CI)		41.7 (27.7, 53.4)
CMH test p-value[c]		p < 0.0001
Mantel-Fleiss Criterion		26.1
Breslow-Day p-value		0.0137
Response Category at Month 12[b], n (%)		
ALP < 1.67× ULN	17 (26.2)	84 (65.6)
≥ 15% decrease in ALP	21 (32.3)	107 (83.6)
Total Bilirubin ≤ 1.0× ULN	50 (76.9)	104 (81.3)

Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT= intent-to-treat; NRS = numerical rating scale; ULN = upper limit of normal
N = total number of subjects, n = number of responders

[a] A subject was designated as a responder if all three of the following conditions were met: (1) ALP < 1.67× ULN; (2) ALP decrease from baseline of ≥ 15%; (3) Total bilirubin ≤ 1.0× ULN.

[b] Subjects with missing data at the specified timepoint for response evaluation were considered nonresponders.

[c] Two-sided p-value for pair-wise comparison was based on the CMH test adjusted for both randomization stratification variables (baseline ALP level: < 350 U/L and ≥ 350 U/L; baseline Pruritus NRS: < 4 and ≥ 4). Breslow-Day test was used to check the homogeneity of treatment effects across stratum. The Mantel-Fleiss criterion was used to assess the validity of the chi-square approximation for the distribution of the Mantel-Haenszel statistic.

The study drug treatment effect was analysed for each stratum (pruritus NRS and baseline ALP) as the Breslow-Day p-value assessing homogeneity of treatment effect across stratum was significant (< 0.05). The results from the stratum analyses were generally consistent with those of the primary analysis of the primary efficacy endpoint showing a higher percentage of responders in the seladelpar compared with the placebo arm, with the following exception:

- A higher percentage of responders in the seladelpar arm compared with placebo was not observed in subjects with ALP ≥ 350 U/L and Pruritus NRS < 4 at baseline [13.3% (2/15) vs 22.2% (2/9)] although interpretation of above result was limited by small sample size.

Key secondary endpoints

ALP normalisation (ALP ≤ 1.0× ULN) at Month 12:

A significantly higher percentage of subjects in the seladelpar arm achieved ALP normalisation (ALP ≤ 1.0× ULN) at month 12 compared with the placebo arm [25% vs 0%; risk diff=25% (95% CI: 18.3, 33.20%), p < 0.0001]. Significant improvement with seladelpar in this endpoint was observed at Month 1 with effects maintained with ongoing treatment throughout the course of the study.

Pruritus NRS at Month 6 in subjects with moderate to severe pruritus at baseline (Pruritus NRS ≥ 4):

Seladelpar treatment led to a statistically significant improvement in Pruritus NRS compared with placebo with an LS mean change at month 6 of 3.2 vs 1.7, respectively [LS mean diff=-1.5 (95% CI: -2.5, -0.5), p=0.0047]). Significantly greater decreases in Pruritus NRS in the seladelpar arm relative to placebo were observed as early as Month 1 and this effect was also seen from Month 6 through Month 12. The difference between the seladelpar and placebo groups was not statistically significant at month 3.

Other secondary and exploratory endpoints

Mean [SD] liver stiffness values at baseline were 9.84 [6.16] kPa for seladelpar vs 8.74 [4.18] kPa for placebo. At Month 12, mean change from baseline in liver stiffness was 0.24 kPa (4.58% change) for subjects receiving seladelpar relative to 1.34 kPa (9.87% change) for those receiving placebo. The mean [SD] baseline values for the ELF scores were comparable between treatment arms (10.16 [1.03] for seladelpar vs 10.23 [0.85] for placebo). There were no notable differences in mean values of the ELF score or its components (HA, TIMP-1, and PIIINP) for the seladelpar arm compared with placebo over the course of the study.

The effect of seladelpar on the PBC-40 QoL questionnaire (total and individual domain scores) in the MSPN analysis set was assessed as a secondary endpoint. There were no meaningful differences in scores for the Fatigue Domain or the PBC-QoL total score between treatment arms over the course of the study. Decreases in the Itch Domain of the PBC-40 QoL questionnaire were greater in the seladelpar arm compared with placebo throughout the course of the study and this was evident as early as Month 1 (p-values for the LS mean differences were < 0.05 from Month 1 through Month 9).

Supportive studies

Study CB8025-31735 (ENHANCE)

This was a Phase III, 52-week placebo-controlled, randomised study to evaluate the safety and efficacy of Seladelpar in subjects with PBC and an inadequate response to or an intolerance to UDCA. The study design objectives were similar to the pivotal Phase III study CB8025-32048.

A total of 207 subjects had liver stiffness measured at baseline (performed by transient elastography which mapped 41 subjects (15.5%) to an Fl score, 30 subjects (11.3%) to an F2 score, 41 subjects (15.5%) to an F3 score, and 18 subjects (6.8%) to an F4 score. Mean liver stiffness for all subjects was 9.94 kPa but was lower in the placebo group (9.28 kPa) than in the seladelpar 10 mg group (11.23 kPa) and seladelpar 5 mg group (9.32 kPa). A liver biopsy was performed within a year from study day 1 as part of the study in 36 subjects (13.6%).

This study was terminated early due to unexpected and unexplained findings in a concurrent Phase 2 study of seladelpar in patients with NASH (CB8025-21730) with findings of atypical and unexpected histological finding following a blinded reading of end-of-treatment (52-week) liver biopsy tissues. The histopathologic findings were ultimately found to be present at baseline and an independent committee and the FDA concluded that there was no safety concern with seladelpar. Following the conclusion of this assessment, the clinical development program was restarted, and the Phase 3 study was redesigned and instituted as CB8025-32048. The NASH program was not carried into Phase 3, though this decision was related to efficacy and unrelated to the histopathologic findings.

The response rate for the primary efficacy composite endpoint after 3 months of treatment was statistically significantly higher in both seladelpar groups compared with placebo [12.5%, 57.1%, and 78.2% in the placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively, p<0.0001].

Study CB8025-21629

This was a Phase II, multicentre, open-label, randomised, parallel group, 8-week dose-ranging (2, 5, and 10 mg once daily) study of seladelpar with a 44-week extension period in 119 subjects with PBC and an inadequate response or intolerance to UDCA.

The primary objective of this study was to evaluate the safety and efficacy of seladelpar over 8 weeks of treatment. The secondary objectives were to evaluate the safety and efficacy of seladelpar over 12, 26, and 52 weeks of treatment and to evaluate the PKs of seladelpar.

A study sample size of 49 subjects per group would have a 90% power to detect a 10% mean difference between the 5 and 10 mg treatment groups based on the use of a 2- sided, 2-sample t-test at the $\alpha = 0.05$ level of significance.

The study had a total of 119 subjects. The primary efficacy endpoint of mean (95% CI) percent change in ALP from baseline to Week 8 was -26.1% (-32.2%, -19.9%), -33.4% (-38.6%, -28.1%), and -41.4% (-45.1%, -37.7%) in the 2, 5 and 10 mg dose groups, respectively. The change in the 10 mg dose group was significantly higher compared with the change in the 2 mg ($p = 0.0021$) and the 5 mg ($p = 0.0024$) dose groups**.**

Study CB8025-31731(ASSURE)

This was a phase III, open-label, long-term study of seladelpar that enrolled subjects who completed study CB8025-21629 or CB8025-31735 (ENHANCE). The primary endpoint for this study was safety. A total of 106 subjects with PBC who were treated in previous studies with seladelpar for approximately 1 year were enrolled. Overall, 46 subjects (16.4%) with cirrhosis at baseline were included in this study [13 subjects (12.4%) from CB8025-32048 and 33 (19.0%) of the legacy and CB8025-21838 studies]. Based on Rotterdam criteria, the majority of subjects (> 83.6%) in the study were considered to have mild disease (normal total bilirubin and albumin), 11.8% had moderately advanced disease (either abnormal albumin or abnormal total bilirubin), and 0.7% had advanced disease (both abnormal albumin and abnormal total bilirubin).

Efficacy in monotherapy subpopulation: Among subjects from CB8025-32048 who were part of the monotherapy subpopulation, 1 crossover subject had enrolled in CB8025-31731-RE at the time of the data cutoff, and this subject achieved the composite biochemical response at both Month 13 and 15. From the continuous seladelpar subjects, 6 had enrolled in CB8025-31731-RE. Of these subjects, 4/6 (66.7%) had achieved a composite response at Month 13, and 3/5 (60%) had achieved a composite response at Month 15. However, interpretation of results in the monotherapy subpopulation is limited by the small number of subjects.

Efficacy in cirrhosis subpopulation: Of the subjects in the cirrhosis subpopulation, 2/9 (22.2%) crossover subjects (from study CB8025-32048) achieved a composite response at Month 12, compared to 7/18 (38.9%) continuous seladelpar subjects.

Safety evaluation summary

The primary evidence of safety of seladelpar in the proposed indication was provided by pivotal Phase III study CB8025-32048 (RESPONSE) in 193 subjects with PBC who had inadequate response or intolerance to UDCA. Supportive evidence for safety of seladelpar in proposed indication was provided by the phase I, II and III studies (CB8025-31735, CB8025-21629, CB8025-31731).

Overall, 1159 subjects received at least 1 dose of seladelpar (293 subjects received placebo) across the clinical pharmacology studies, placebo-controlled double-blind studies in PBC, uncontrolled open-label studies in PBC, and studies of indications other than PBC. Mean (SD)

duration of seladelpar treatment overall was 39.09 (49.72) weeks. Furthermore, 314 PBC patients were exposed to 10 mg seladelpar for ≥ 52 weeks.

Adverse events (AEs)

Overall, 166 of the 193 subjects (86.0%) in the pivotal study had at least 1 Treatment-Emergent Adverse Event (TEAE) during the study with similar incidence in the seladelpar and placebo groups (86.7% vs 84.6%). The most common System Organ Classes (SOCs) for TEAEs in this study were infections and infestations (48.2%), gastrointestinal disorders (33.7%), musculoskeletal and connective tissue disorders (25.4%), general disorders and administration site conditions (18.7%), skin and subcutaneous tissue disorders (18.1%), and nervous system disorders (16.1%). Within most SOCs, the incidence of TEAEs was similar between the seladelpar 10 mg and placebo groups with the following exceptions: injury, poisoning, and procedural complications (13.3% vs 6.2%), and blood and lymphatic system disorders (11.7% vs 4.6%).

The incidence of treatment-related TEAEs as assessed by the Investigator was slightly higher in the seladelpar compared to the placebo group (17.2% vs 12.3%). The most common (≥ 2 subjects) treatment-related TEAEs in the seladelpar 10 mg group were headache (3.1%), diarrhoea (2.3%), and abdominal distension, dizziness, nausea, and vomiting (1.6% each).

Treatment-related TEAEs that occurred at a ≥ 2% higher incidence in the seladelpar group compared with the placebo group were headache (3.1% vs 0%) and diarrhoea (2.3% vs 0%). None of the treatment-related TEAEs were reported as Grade ≥ 3 or serious.

Deaths and other serious adverse events (SAEs)

There were no deaths in the pivotal study.

The incidence of treatment-emergent SAEs was similar in the seladelpar and placebo groups [9 (7.0%) subjects vs 4 (6.2%) subjects] and none of these SAEs were considered treatment-related. All treatment-emergent SAEs were reported for one subject each, with the exception of COVID-19, which occurred in one subject in each group.

None of the treatment-emergent SAEs were considered to be treatment-related. Three subjects had a treatment-emergent SAE that led to discontinuation of study drug: Grade 3 papillary thyroid cancer and Grade 3 coagulopathy in the seladelpar group, and Grade 4 suicide attempt in the placebo group.

A total of 7 (3.6%) subjects discontinued treatment due to TEAEs, including 4 subjects in the seladelpar group (3.1%) and 3 subjects in the placebo group (4.6%). All TEAEs leading to treatment discontinuation occurred in 1 subject each**.** Treatment-related TEAEs leading to discontinuation of study drug occurred in 2 subjects in the seladelpar group (disease progression in 1 subject and liver function test increased in 1 subject) and none in the placebo group.

From the pooled safety analyses, the exposure-adjusted subject incidence for muscle-related, renal related, pancreatic-related, and cardiovascular related TEAEs were similar between placebo, seladelpar 10 mg, and seladelpar ≤ 10 mg. However, the exposure-adjusted subject incidence of treatment-related TEAEs, pruritus-related TEAEs, and liver-related TEAEs was lower in subjects treated with seladelpar 10 mg and subjects treated with seladelpar ≤ 10 mg compared to the placebo group.

The exposure-adjusted subject incidence of TEAE with fatal outcome was 0.15 vs 0 per 100 subject-years but interpretation is limited as there was only one TEAE with a fatal outcome (in study CB8025-31731). A late-breaking treatment-emergent SAE leading to death was reported

after the data cutoff date of 29 Jun 2023 (the fatal event of autoimmune haemolytic anaemia was considered unlikely related to study drug).

Evaluation of issues with possible regulatory impact

Liver function and liver toxicity

Overall, 8 (6.3%) subjects in the seladelpar 10 mg group and 6 (9.2%) in the placebo group experienced a liver-related TEAE. 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.

Treatment-related hepatic TEAEs were reported in 2 subjects in the seladelpar group (blood bilirubin increased and liver function test increased) and 1 subject in the placebo group (liver function test increased). Liver-related TEAEs leading to discontinuation of the study drug were only for 1 subject each in the seladelpar (liver function test increased) and placebo group (hyperbilirubinaemia). Three subjects were identified as meeting potential Hy's Law criteria: 2 in the placebo group and 1 in the seladelpar group. However, none of these cases were consistent with Drug Induced Liver Injury (DILI) related to study drug.

In study CB8025-32048, 27 (14%) subjects (14.1% and 13.8% of subjects in the seladelpar and placebo groups, respectively) had cirrhosis at baseline and the safety profile of seladelpar in these subjects was similar to that observed in those without cirrhosis and generally similar to placebo. It is important to note that subjects with decompensated cirrhosis (CP-B or CP-C) were not evaluated in the pivotal study.

Renal function and renal toxicity

No renal-related TEAEs (defined using broad Acute renal failure SMQ) were reported for the pivotal study.

More subjects in the seladelpar group had eGFR decreases of ≥ 25% from baseline than in the placebo group [n=12 (9.4%) vs n=1 (1.5%)]. There were no shifts of ≥ 3 severity grades in creatinine and no shifts of ≥ 2 severity grades in eGFR levels. Time to onset was variable and the majority of these eGFR decreases resolved within a few months with ongoing treatment.

Other clinical chemistry, vital signs and clinical examination and immunogenicity events

There were no safety concerns identified related to muscle or pancreatic toxicity.

Shifts from baseline of ≥ 2 severity grades in CK were experienced by 1 (0.8%) subject in the seladelpar 10 mg group (a 2-grade shift) and 1 (1.5%) subject in the placebo group (a 4-grade shift); these shifts were transient, and levels returned to normal. Mean absolute values and percentage changes in haematology parameters from baseline were generally similar between treatment groups. Shifts of ≥ 2 grades from baseline in haematology parameters were observed in a similar proportion of subjects between treatment groups. The incidence of shifts of ≥ 2 grades from baseline in select haematology parameters were similar in the seladelpar 10mg vs placebo groups [18 (14.1%) vs 8 (12.3%) subjects with neutrophil count decreased most common in both groups (8.6% vs 10.8%).

There were no clinically meaningful changes in vital signs parameters (temperature, heart rate, respiratory rate, blood pressure) in either treatment group.

No safety concerns were identified in pivotal or supportive studies regarding immunological events.

Post marketing experience

Accelerated approval (equivalent to Australia's provisional registration) for seladelpar was obtained in the USA on 14 August 2024 and the sponsor has stated (in the EU-RMP) that no new safety information was identified to date from the post-marketing experience.

Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
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	✓	✓‡	✓	–

‡ Study CB8025-31731-RE (ASSURE)

The summary of safety concerns in the ASA aligns with the EU-RMP and is satisfactory from an RMP perspective.

Routine and additional pharmacovigilance activities are proposed. Additional pharmacovigilance activity includes study CB8025-31731-RE (ASSURE) to further characterise the important potential risk and missing information. At round 2, study CB8025-21838 has been removed due to completion. The pharmacovigilance plan is acceptable from an RMP perspective.

Only routine risk minimisation activities have been proposed, and the risk minimisation plan is acceptable from an RMP perspective.

Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

The sponsor is seeking to register seladelpar for the proposed indication:

Seladelpar is indicated for the treatment of primary biliary cholangitis (PBC), including pruritus, in adults in combination with ursodeoxycholic Acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.

The sponsor has sought a full registration of seladelpar in Australia. Seladelpar has only been granted conditional marketing approval by the EMA and was granted accelerated approval by the FDA. Both the EMA and the FDA have requested evidence for seladelpar to demonstrate efficacy for hepatic survival endpoints before full approval. This is particularly relevant as obeticholic acid (Ocaliva) had failed to demonstrate benefit in a confirmatory phase 4 study COBALT evaluating the clinical outcomes of obeticholic acid in PBC patients. However, it is noted that the trial was underpowered, and the majority of the patients had advanced liver disease. It is also noted that seladelpar is a selective PPARδ agonist and thus is mechanistically different to obeticholic acid, which is a farsenoid x receptor agonist. Therefore, the issues affecting obeticholic acid may not be directly associated with the benefit risk profile of seladelpar.

The single pivotal study CB8025-32048 (RESPONSE) enrolled adult patients with PBC who have been on UDCA for at least 12 months or intolerant to UDCA. In Study CB8025-32048 seladelpar treatment led to a statistically significant biochemical response at Week 52, defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%. At week 52, the proportion of responders were 79/128 (61.7%) in the seladelpar group and 13/65 (20%) in the placebo group, a difference of 41.7% (95% CI: 27.7, 53.4, p<0.0001). However biochemical response remains a surrogate marker for clinical outcomes in PBC.

The latest EMA guidance on PBC which was reviewed in the evaluation of seladelpar states 'at present, it has only been demonstrated for the natural history, as well as for UDCA, that the reduction of ALP and bilirubin leads to an overall improved outcome with regard to the development of end-stage liver disease, decompensation, liver transplantation and death. Whereas on one hand a primary endpoint based on these markers is considered acceptable, on the other hand it needs to be supported by additional secondary clinical endpoints.'

Seladelpar was able to demonstrate that the first multiplicity controlled key secondary endpoint, normalisation of ALP at week 52, was reached by 32/128 (25%) of the seladelpar-treated participants and 0/65 (0%) of the placebo treated participants (difference 25% [18.3, 33.2], p<0.0001). A small reduction in bilirubin levels was also demonstrated, however the majority of PBC patients had normal bilirubin levels at baseline.

While ALP and bilirubin levels are surrogate endpoints for PBC clinical outcomes, liver specific guidelines support the use of ALP and bilirubin as predictors of prognosis as well as in prognostic models. Specifically, ALP, which has been shown to correlate with ductopenia and liver inflammation, is thought to be a reliable predictor of prognosis, and validated prognostic models such as the GLOBE score developed for PBC includes bilirubin and ALP as variables, along with age, albumin and platelet count (AASLD practice guidance 2019 and 2021). The standard clinical practice of monitoring response to therapy is also primarily based on ALP and bilirubin monitoring, with classification of patients as responders or non-responders based on these two biochemical markers at scheduled follow-up timepoints. Prognostic scores such as the GLOBE score are then used to predict patients at increased risk of progression to death or liver transplantation. UCDA, the first line therapy for PBC, was approved for PBC treatment based on trials assessing bilirubin and ALP levels.

The EMA guidance also recommends use of supportive endpoints such as symptomatic response, non-invasive tests and liver histology. The sponsor studied change from baseline to month 6 in weekly averaged pruritus NRS in patients with a baseline pruritus score of ≥4 which was a second multiplicity controlled key secondary endpoint, which was significantly better in the

seladelpar group than the placebo group with a LS mean (SE) -3.2 (0.28) vs -1.7 (0.41), difference -1.5 (-2.5, -0.5), P=0.0047) compared to placebo. Additionally exploratory endpoints of changes in the Itch Domain of the PBC-40 QoL from baseline to month 6 favoured seladelpar. The sponsor provided evidence to support the responsiveness, test-retest reliability, convergent validity, discriminant validity, and known-groups validity for the Pruritus NRS in patients with PBC. There was no significant change in liver stiffness or histology results between treatment groups although patient numbers with these results were small.

Overall, the pivotal study did not provide efficacy data for measurable clinical outcomes in PBC such as time to progression to end stage liver disease as recommended in the updated EMA reflection for PBC. Additionally, efficacy data beyond one year are available from open-label studies of seladelpar. Seladelpar has been granted accelerated approval in the United States (equivalent to our provisional registration) and conditional marketing authorisation in Europe. These decisions reflect the fact that the impact of seladelpar on long-term liver survival for patients with PBC is still uncertain. To support the long-term efficacy and data on event-free survival the sponsor is conducting an ongoing 3-year study CB8025-41837, which includes patients with moderate hepatic impairment. It is also noted by the Delegate that at the time of the conception of the clinical program the EMA guidance had not yet been updated and this has not yet been adopted by the TGA.

The sponsor proposes to include 'pruritus' in the wording of the indication. This is not appropriate as pruritus was studied as a secondary endpoint and while efficacy and safety results can be outlined in the product information, it should not in general be included in the indication.

The pivotal study duration was 1 year, in contrast to the recommended 2 years duration with the EMA reflection paper published in 2023. The sponsor stated that this updated EMA guidance was published after the commencement of the pivotal trial, and that twelve months was selected as the study duration after discussions with multiple stakeholders with the FDA and EMA. The sponsor also discussed that this length of time has been standard for the primary endpoint used in registrational PBC trials for other second-line agents.

Consistent with the relative rarity of UDCA intolerance, the pivotal study only included a small number of patients who were UDCA intolerant (6.2%); 8 received seladelpar and 4 received placebo. In the pooled analysis there were 22 patients in total, of which 16 received seladelpar. Eight patients (50%) achieved a biochemical response compared to 1 (17%) in placebo, supporting the inclusion of seladelpar as a monotherapy for PBC patients despite the limited number of patients studied. The sponsor also studied the efficacy of the monotherapy subpopulation in the open-label safety study CB8025-31731-RE.

In the pivotal study, seladelpar had a relatively safe safety profile and a lower number of subjects experienced at least 1 liver-related TEAEs compared to the placebo group (8 (6.3%) vs 6 (9.2%)).

Of the 33 subjects from the legacy and CB8025-21838 studies who enrolled in study CB8025-31731-RE, 31 subjects (93.9%) with cirrhosis were classified as Child-Pugh A and 2 subjects (6.1%) as Child-Pugh B; 8 subjects (24.2%) had portal hypertension. However, there was no safety data for seladelpar use in patients with moderate or severe hepatic impairment (Child Pugh Class B and C). The sponsor has addressed this in section 4.2 of the PI regarding special populations, where it is stated that seladelpar is not recommended for patients with decompensated cirrhosis and treatment discontinuation should be considered for patients who progresses to moderate or severe hepatic impairment. Additionally, the sponsor has commitments to the EMA as part of the conditional approval of seladelpar to provide long-term

safety outcomes in patients with moderate hepatic impairment in the 3-year study CB8025-41837 (AFFIRM).

Proposed action

Pending advice from the Advisory Committee for Medicines, I propose to approve the registration of seladelpar for the following indication, subject to conditions and agreement on an appropriate PI:

> *Seladelpar is indicated for the treatment of primary biliary cholangitis (PBC), in adults in combination with ursodeoxycholic Acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.*

Proposed conditions of registration

The interim and final results of the ongoing phase III study (CB8025-41837) should be provided to the TGA when they are available to allow appropriate evaluation of updated efficacy and safety data.

Independent expert advice

The Delegate received the following independent expert advice.

Advisory Committee on Medicines considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***What is the ACM's opinion regarding the selection of primary endpoint for the single pivotal phase III trial CB8025-32048 and its suitability to demonstrate long term efficacy for seladelpar?***

The ACM advised that the composite endpoint of ALP reduction and bilirubin normalisation is a suitable endpoint as a lower ALP (<1.67 x the upper limit of normal) is associated with improved clinical outcomes and a lower risk of clinical progression. The ACM also noted that ALP reduction has been used as a primary endpoint in studies investigating similar medicines used to treat PBC, such as the ELATIVE (elafibranor) and POISE (obeticholic acid) studies.

2. ***Does ACM perceive that the totality of evidence provided by the sponsor is sufficient for the full registration for seladelpar (noting that the TGA does not have the regulatory pathway to allow the submission to result in a provisional registration outcome)?***

The ACM were satisfied that the results of ten Phase I, two Phase II, and three Phase III studies were sufficient to support the full registration of Livdelzi. The ACM considered the amount of available evidence to be comparable to that of other second line agents for PBC.

3. ***Does the ACM support that the sponsor should provide results of any ongoing phase 3 studies to the TGA when available as a condition of registration?***

The ACM held the view that the data to date did not show a change in the long-term clinical outcomes of PBC when treated with Livdelzi. Therefore, the ACM were supportive that all

available data should be shared with the TGA when the ongoing, long-term studies have concluded. The ACM were satisfied that this should be a condition of registration of Livdelzi.

4. ***What is the ACM's advice regarding the proposal by the sponsor to include seladelpar as monotherapy in adults unable to tolerate UDCA in the indication?***

Livdelzi is approved as a monotherapy in the US, EU and UK.

The ACM reviewed the limited data examining the biochemical response to Livdelzi monotherapy that was contained in the RESPONSE and ENHANCE studies. These results showed an appropriate response to the monotherapy at 3 and 12 months.

The ACM noted that the rare patients unable to tolerate UDCA would have a lack of treatment options which would likely lead to disease progression and potentially death. The ACM were satisfied that the available data, although limited, was acceptable to allow the use of Livdelzi as a monotherapy in this population.

5. ***What is the ACM's advice regarding the proposal by the sponsor to include 'pruritus' in the indication?***

The ACM discussed the three itch scales used in the RESPONSE trial including the NRS, 5-D itch scale, and itch section of the PBC 40 questionnaire. The ACM noted that these scales have been validated in prior studies on PBC.

In the RESPONSE trial, significant improvements were seen in the NRS and 5-D itch scores in participants treated with Livdelzi. No improvements were seen in the PBC 40 itch scores. This data was compared to results of trials using elafibranor that used the same scales, in these; the elafibranor arm saw improvements in the 5-D itch score, and the PBC 40 itch scores, but not the NRS.

On balance, the ACM held the view that decisions to use Livdelzi should be based on hepatic biochemical parameters and not pruritus as is standard for other second-line agents. The ACM advised that pruritus was not necessary to include in the indication. Additionally, the ACM noted that there is no clear difference in pruritus reduction between the various PPAR agonists, and different indications between them could be misleading.

6. ***Please discuss any other aspect of the submission deemed relevant.***

The ACM had no additional advice to provide on this submission.

Advisory committee conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Seladelpar is indicated for the treatment of primary biliary cholangitis (PBC) in adults 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.*

Assessment outcome

Based on an assessment of quality, safety, and efficacy, the TGA decided to register Livdelzi (seladelpar) 10mg capsule bottle. The approved indication for this therapeutic good is:

> *Livdelzi 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.*

Specific conditions of registration

- Livdelzi is to be included in the Black Triangle Scheme. The PI and CMI for Livdelzi must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The Livdelzi EU-Risk Management Plan (RMP) (version 1.0, dated 12 December 2024, data lock point 31 January 2024), with Australia-Specific Annex (ASA) (version 0.2, dated July 2025), included with submission PM-2024-05956-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.
- The interim and final results of the ongoing phase III study (CB8025-41837) should be provided to the TGA when they are available to allow appropriate evaluation of updated efficacy and safety data.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au