12 December 2024
EMA/12861/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Seladelpar Gilead

International non-proprietary name: seladelpar

Procedure No. EMEA/H/C/004692/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Abbreviation	Definition
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
BCS	Biopharmaceutics classification system
BHT	Butylated hydroxytoluene
BMI	Body mass index
C4	7a-hydroxy-4-cholesten-3-one
CEP	Certificate of suitability to the monographs of the European Pharmacopoeia
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	Clinicopathological review committee
CQA	Critical quality attribute
CrCl	Creatinine clearance
CSR	Clinical study report
CTAB	Cetyltrimethylammonium bromide
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome p450
DDI	Drug-drug interaction

DSIC	Drug substance in capsule
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
EMEA	Europe, the Middle East, and Africa
EOT	End of treatment
E-R	Exposure-response analysis
EU	European Union
FDA	Food and Drug Administration
FT-IR	Fourier transform infrared spectroscopy
GC-MS	Gas chromatography mass spectrometry
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HS-GC	Headspace gas chromatography
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control
KF	Karl Fischer titration
LDPE	Low density polyethylene
PBPK	Physiologically based pharmacokinetic
PDE	Permitted daily exposure
Ph. Eur	European Pharmacopoeia
PP	Polypropylene
RH	Relative humidity
SmPC	Summary of product characteristics
TSE	Transmissible spongiform encephalopathy
UHPLC	Ultra-high performance liquid chromatography

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences Ireland Unlimited Company submitted on 10 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Seladelpar Gilead, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 October 2019.

Seladelpar Gilead, was designated as an orphan medicinal product EU/3/17/1930 on 16 October 2017 in the following condition: Treatment of primary biliary cholangitis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Seladelpar Gilead as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/seladelpar-gilead.

The applicant applied for the following indication: *Livdelzi is a peroxisome proliferator receptor delta (PPARδ) activator indicated for the treatment of primary biliary cholangitis (PBC) including pruritus in adults without cirrhosis or with compensated cirrhosis (Child-Pugh A) in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.*

1.2. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0192/2019 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation and accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance seladelpar, contained in the product as seladelpar lysine dihydrate to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Seladelpar Gilead was granted eligibility to PRIME on 16 October 2017 in the following indication:

Treatment of Primary Biliary Cholangitis (PBC) in patients who do not tolerate or respond to UDCA or do not respond to UDCA/OCA combination treatment.

Upon granting of eligibility to PRIME, Kristina Dunder was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 20 February 2017. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

1. Quality aspects:

- Starting materials – recommended that CymaBay seek Scientific Advice (CymaBay tentatively plans to request advice at the August Meeting of SAWP)
- Change of pharmaceutical form – recommended that a bridging bioavailability be performed with the new pharmaceutical form
- EU requirements on manufacturing sites and GMP compliance – indicated that EU GMP requirements would need to be met

2. Nonclinical aspects:

- Carcinogenicity – the applicant was advised that the assessment of the relevance of tumour findings will be of importance. It was recommended to include data on the role of PPARδ in the liver tumour MOA
- The nonclinical assessor highlighted that in general, the potency and selectivity were important in assessing the relevance of the nonclinical findings.
- Recommended seeking Scientific Advice on the adequacy of the Nonclinical Development Programme (CymaBay tentatively plans to request advice for the Nonclinical Development Programme and the Clinical Development Programme at the August Meeting of SAWP)

3. Clinical aspects:

- A number of points were highlighted for the applicant to consider in the planned phase 3 pivotal study and future scientific advice:
- Choice of dose – the Rapporteur highlighted the importance of dose-finding study was

supportive of evaluating both a higher and lower dose in the on-going study as well as expanding enrolment.

- Choice of control arm – while a placebo comparator group would be preferred from a regulatory perspective in view of characterising the safety profile of the product, Health Technology Assessment group (HTA) may prefer an active control. This would also support discussion on the maintenance of the orphan designation and significant benefit criteria. The applicant was recommended to consider parallel EMA/HTA Scientific Advice (CymaBay tentatively plans to request advice for the Nonclinical Development Programme and the phase 3 Clinical Development Programme at the August Meeting of SAWP)
- Target population: the definition of UDCA inadequate responders was suggested as a topic for discussion in scientific advice.

4. Regulatory aspects:

- Type of marketing authorisation: the applicant was advised to seek scientific advice on the strategy to apply for conditional marketing authorisation
- Paediatric investigation plan: the PDCO representative agreed that a waiver for PBC would be relevant, with a proposal for other indications that are relevant to the paediatric population based on the mechanism of action.
- Orphan designation and criteria of significant benefit: orphan designation may be requested based on the assumption of significant benefit potentially being increased efficacy (ALP) and better safety profile (prevention/reduction in pruritus). The applicant was advised to discuss the issue of significant benefit in the upcoming SA and whether a comparator arm will be required to support the maintenance at time of designation or whether other sources of comparison may be used.
- The extension of the on-going phase 2 study beyond 26 weeks should be requested at the national level
- Discussed potential use as second line add on therapy for patients with either an inadequate response to UDCA or UDCA/OCA defined as ALP > 1.67 X ULN and patients not adequately controlled defined as ALP > ULN and < 1.67 X ULN. The later patients not currently indicated for treatment with OCA, could then be evaluated in a clinical trial utilizing a placebo comparator.

1.7. Scientific Advice

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
9 August 2017	EMEA/H/SA/3656/1/2017/SME/PR/I	*Dr Andreas Kirisits and Dr Elmer Schabel*
15 February 2018	EMEA/H/SA/3656/2/2017/PA/SME/PR/III	*Dr Kerstin Wickström and Prof. Brigitte Blöchl-Daum*
30 April 2021	EMA/SA/0000061032	*Johannes Hendrikus Ovelgonne and Anna Vikerfors*

The Scientific Advice pertained to the following *quality, non-clinical, and clinical* aspects:

- Starting materials, monitoring of potential genotoxic impurities,
- Planned non-clinical programme
- Overall clinical development strategy, Phase 3 plans: placebo control, primary and secondary efficacy endpoints, study population, statistical analysis plan, dose regimen, study duration, sample size, single pivotal study approach, evidence generation to support potential conditional marketing authorisation and conditions for full marketing authorisation, safety database, information on patients with hepatic and renal impairment, characterisation of drug-drug-interactions
- Evidence to support significant benefit vs. other orphan medicinal products

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Thalia Marie Estrup Blicher

The application was received by the EMA on	10 February 2024
The procedure started on	29 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 May 2024
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	31 May 2024
The PRAC Rapporteur's Assessment Report was circulated to all PRAC and CHMP members on	3 June 2024 and 11 June 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 August 2024
The following GCP inspection(s) were requested by the CHMP, and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: A GCP inspection at three sites, 2 clinical sites and the sponsor site in Mexico and the USA between 03 June and 23 August 2024. The outcome of the inspection carried out was issued on	03 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 November 2024

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 November 2024 05 December 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Seladelpar Gilead on	12 December 2024
The CHMP adopted a report on similarity	12 December 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	12 December 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication was initially "*Livdelzi is a peroxisome proliferator receptor delta (PPARδ) activator indicated for the treatment of primary biliary cholangitis (PBC) including pruritus in adults without cirrhosis or with compensated cirrhosis (Child-Pugh A) in combination with ursodeoxycholic acid*
(UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA".

2.1.2. Epidemiology

PBC is a serious and potentially life-threatening autoimmune disease of the liver characterised by inflammation and destruction of intrahepatic bile ducts resulting in cholestasis and accumulation of toxic bile acids (Gulamhusein 2020). It can progress to liver fibrosis, cirrhosis, and hepatic failure, and is one of the top 6 indications for liver transplantation in the EU and US (Harms 2019), despite being a rare disease.

The estimated prevalence of PBC in North America, Europe, and the Asia-Pacific region varies from 1.91 to 40.2 per 100,000 persons and incidence varies from 0.23 to 5.31 per 100,000 persons, with the incidence of PBC increasing over time in North America and Europe. PBC occurs more frequently in women and presents most often in middle age, with peak incidence in the fifth decade of life (Kaplan 2005).

2.1.3. Aetiology and pathogenesis

PBC is an autoimmune liver disease characterised by impaired bile flow (cholestasis) and accumulation of toxic bile acids (Gulamhusein 2020; Lleo 2020). Serologically, PBC is characterised by the presence of AMAs in nearly all patients (Selmi 2010). The liver histopathology of patients with PBC is characterised by portal inflammation and immune-mediated destruction of intrahepatic bile ducts. The loss of bile ducts leads to decreased bile secretion and the retention of

hydrophobic bile acids within the liver, resulting in hepatocellular injury, fibrosis, cirrhosis, and eventually, liver failure.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Approximately 50% to 60% of those diagnosed with PBC are asymptomatic at diagnosis. Overt symptoms develop within 2 to 4 years in most patients, although one-third of patients may remain symptom-free for years (EASL 2017). Clinical symptoms include pruritus, which can be severe, and for which there are no specifically approved therapies. Cholestatic pruritus affects up to 70% of patients (Carey 2015) and can be extremely debilitating (Rishe 2008). Other features of PBC include coexisting autoimmune diseases, hypercholesterolemia, and bone loss, including osteoporosis (EASL 2017; Kumagi 2008). Hepatomegaly, splenomegaly, and abdominal pain are also common in PBC patients.

2.1.5. Management

The first-line therapy for PBC is UDCA, a noncytotoxic bile acid that has been the mainstay of treatment for more than 20 years (Poupon 1997). However, despite receiving UDCA, up to 40% of patients have persistent elevation of ALP and/or bilirubin and are considered inadequate responders (Corpechot 2008). Intolerance to UDCA may also occur and is seen in up to 5% of patients (Invernizzi 2017). Obeticholic acid (Ocaliva, OCA) was conditionally approved by the EMA in 2016 based on the surrogate endpoints of ALP levels and total bilirubin levels in patients with PBC who were inadequate responders or were intolerant to UDCA (Ocaliva SmPC 2023). In June 2022, the EU SmPC for OCA was revised to contraindicate its use in PBC patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C), or a prior decompensation event (Ocaliva SmPC 2023). Following a procedure under Article 20 of Regulation (EC) No. 726/2004 to reassess the benefit/risk balance for OCA based on the failure of post-approval studies designed to confirm the clinical benefit the Marketing authorisation of Ocaliva was revoked due to the failure to show effect on clinically important events. A new treatment, Iqirvo (elafibranor), recently (sept 2024) received a conditional marketing authorisation for PBC not responding to / intolerant to UDCA by showing a beneficial effect on biomarkers, but without significant effect on pruritus. Thus, many patients with PBC and cirrhosis may still have limited treatment options aside from UDCA.

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 significant side effects. There remains an unmet need for a therapy that both slows progression of disease and improves clinical symptoms.

2.2. About the product

Seladelpar is a novel PPARδ agonist, that affects transport, storage, and metabolism of lipids. PPARδ is a nuclear receptor expressed in the liver and other tissues. Activation of PPARδ 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.

The initially proposed indication was "*Livdelzi is a peroxisome proliferator receptor delta (PPARδ) activator indicated for the treatment of primary biliary cholangitis (PBC) including pruritus in adults without cirrhosis or with compensated cirrhosis (Child-Pugh A) 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 posology is:

The recommended dose of Seladelpar Gilead is 10 mg once daily.

Special populations

Elderly

Clinical studies included patients aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and subjects less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.

Renal impairment

No dose adjustment of Seladelpar Gilead is required for patients with mild, moderate and severe renal impairment. Patients with end-stage renal disease on dialysis have not been studied (see Section 5.2).

Hepatic impairment

No dose adjustment is required in PBC patients with mild hepatic impairment (Child-Pugh A).

Safety and efficacy of Seladelpar Gilead have not been established in PBC patients with decompensated hepatic impairment (Child-Pugh B or C). No dose recommendation can be given for patients with moderate and severe hepatic impairment (Child-Pugh B or C) (see Section 5.2).

Monitoring patients with cirrhosis for evidence of decompensation or for progression to Child-Pugh B or C hepatic impairment should be considered as clinically warranted.

Paediatric population

There is no relevant use of Seladelpar Gilead in the paediatric population in the treatment of PBC.

Method of administration

Oral use. The capsules can be taken with or without food.

The capsules must be swallowed whole.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. CHMP conclusions based on the argumentation and data provided at that stage were as follows:

The surrogacy of the biochemical markers is not established. To support the proposed indication "treatment of patients with PBC", data on clinically relevant liver related endpoint would usually be expected (e.g. time to diagnosis of cirrhosis, decompensation events of cirrhosis, MELD score of > 14 defining a high risk of liver related death, as well as liver transplantation and death). However, no information regarding the results of these endpoints/data collections have been presented.

The applicant argued that seladelpar offers added value over current standard of care (UDCA and OCA) in the treatment of PBC in terms of superior efficacy and improved tolerability. However, regarding efficacy, any conclusions based on indirect comparison should be regarded with caution and the provided data does not allow for a rigorous assessment of the indirect comparison.

The applicant provided data on pruritus to support the proposed indication "treatment of patients with PBC including pruritus". However as stated in the reflection paper for chronic non-infectious liver diseases including PBC (EMA/CHMP/299976/2018) currently, no fully validated patient reported outcome (PRO) for pruritus in PBC exists and Cholestyramine is an approved therapy for moderate-severe cholestatic pruritus in several EU countries.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules containing 10 mg of seladelpar as active substance. The product contains the L-lysine dihydrate salt.

Other ingredients are:

Capsule contents: mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide and butyl hydroxytoluene.

Capsule shells: gelatin, titanium dioxide, black iron oxide, red iron oxide, yellow iron oxide (all E172), and indigo carmine (E132).

Black printing ink: Shellac (E904), propylene glycol (E1520), potassium hydroxide (E525) and black iron oxide (E172).

White printing ink: Shellac (E904), propylene glycol (E1520), sodium hydroxide (E524), povidone (E1201) and titanium dioxide.

The product is available in high density polyethylene (HDPE) bottles closed with polypropylene (PP) child resistant caps containing induction seals as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of seladelpar is [4-({(2*R*)-2-ethoxy-3-[4-(trifluoromethyl)-phenoxy]propyl}sulfanyl)-2-methylphenoxy]acetate corresponding to the molecular formula $C_{21}H_{23}F_3O_5S$. It has a relative molecular mass of 444.5 g/mol. The L-lysine dihydrate form has a molecular mass of 626.7 g/mol and the following structure:

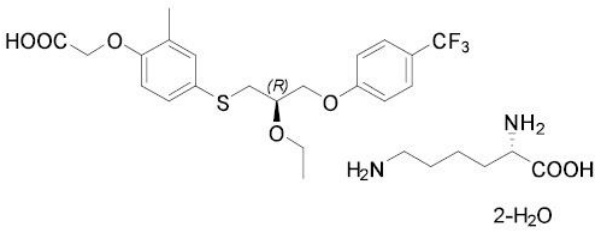


Figure 1: active substance structure

The chemical structure of seladelpar lysine dihydrate was elucidated by a combination of elemental analysis, ultraviolet spectroscopy, infrared spectroscopy, electrospray ionisation mass spectrometry, nuclear magnetic resonance spectroscopy and x-ray powder diffraction. The solid-state properties of

the active substance were measured by dynamic vapour sorption, thermogravimetric analysis and differential scanning calorimetry.

The active substance is a white to off-white crystalline solid, slightly hygroscopic, freely soluble in neutral and basic aqueous media, but solubility decreases below pH 6.

The manufacturing process consistently produces a single polymorphic form which is stable other than in extremes of heat and humidity.

Seladelpar contains a single stereogenic centre which is introduced in one of the starting materials and is carried through the synthetic process unchanged. The lysine counter ion is introduced as a single enantiomer. Chiral purity is routinely controlled in the active substance specifications.

Manufacture, characterisation and process controls

Satisfactory GMP documentation has been provided for sites used in the manufacture of active substance.

The process is convergent and uses 3 starting materials defined according to ICH Q11 and in line with scientific advice provided in 2017. The applied specifications and test methods are acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The process impurities that may be present in the active substance, and therefore carried over into the finished product, have been identified. The known and potentially mutagenic impurities that may be present in the active substance are listed and a detailed assessment and controls are outlined. Spike/purge studies on potential impurities were conducted to better understand the factors responsible for their formation and the ability of the process to purge them. The control strategy with respect to impurities is acceptable.

Changes were made throughout development to improve the process. All changes made during process development are justified with respect to the impact on quality. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in two low density polyethylene (LDPE) bags with twist ties inside a HDPE keg. Materials comply with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for appearance, identity, assay, impurities, chiral purity, water content, residue on ignition, elemental impurities, residual solvents, L-lysine content and particle size distribution.

The specifications, test methodology, and limits have been set based on ICH guidance, pharmacopoeial requirements, and based on process capability. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies. The omission of polymorphic form and microbial limit tests has been adequately justified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 14 batches of the active substance up to production scale are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from seven production scale batches of active substance from the proposed manufacture stored in the intended commercial package for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Additional stability data is available for batches stored in the refrigerator or at 30ºC/75% RH. The parameters tested were appearance, assay, impurities, water content and particle size in line with the shelf-life specifications. Polymorphic form, chiral purity and microbial limits were also tested. All tested parameters were within the specification limits and no trends were observed. The results justify the omission of tests for polymorphic form, chiral purity and microbial limits from the post-approval stability protocol.

The effects of forced degradation, including photostability in accordance with ICH Q1B has been evaluated. The active substance is sensitive to extreme heat and oxidative conditions but minimally sensitive to light. Based on the overall results, the UHPLC method for identification, assay and impurities is shown to be stability indicating and capable of adequately detecting degradation products.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months stored in the proposed container at 20-25°C, protected from light.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The product consists of size 1 (19.4 mm x 6.9 mm) hard gelatin capsules, with a light grey body and a dark blue cap, printed with "CBAY" in white ink on the cap and "10" in black ink on the body. Each capsule contains 14.1 mg seladelpar lysine dihydrate equivalent to 10 mg seladelpar.

The primary objective of formulation development was to produce a stable immediate release formulation containing seladelpar as active substance. The lysine dihydrate salt was selected for development. A single polymorphic form is produced which is stable to humidity within the range 1-80% relative humidity (RH). The active substance is highly permeable and freely soluble at neutral and basic pH but becomes increasingly insoluble as pH drops, being completely insoluble at pH 2.5 and below. It is considered borderline BCS Class I/II.

The initial formulation used during Phase 1 clinical studies consisted of neat seladelpar for reconstitution. The proposed commercial formulation was developed considering the intended 10 mg dose and consists of a dry granulated blend of the active substance and excipients filled into a capsule. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The active substance is sensitive to oxidation, a process enhanced by some excipients. Therefore, butylated hydroxytoluene (BHT) is included as an antioxidant. The amount present has been adequately justified.

The applicant presented the quality target product profile of the product and defined the critical quality attributes (CQAs) as dissolution, assay, uniformity of dosage units (content uniformity) and related substances.

The development of the dissolution method and demonstration of discriminatory power were described. The applicant developed a physiologically based pharmacokinetic (PBPK) model has which is detailed in the clinical section. It has been shown that the active substance dissolves rapidly in the small intestine and is quickly absorbed. This is shown for both neat active substance in capsules and the intended commercial formulation which are bioequivalent. Thus, a discriminatory dissolution method is not necessary. Nonetheless, the CHMP raised a major objection as the initially proposed specification limit and time (90 minutes) was considered far too wide for an immediate release capsule. The applicant tightened the limit to Q=75% at 60 minutes and added a second limit of Q=45% at 30 minutes. The developed method with the revised specification limits is considered adequate for quality control purposes and the major objection is considered resolved.

The primary packaging is HDPE bottles closed with PP child resistant caps containing induction seals. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Satisfactory GMP documentation has been provided for sites manufacturing the drug product.

The manufacturing process consists of 5 main steps: blending of the active substance with intra-granular excipients, dry granulation, blending with extra-granular excipients, encapsulation and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process will be validated on 3 consecutive batches of finished product prior to commercialisation. The submitted process validation scheme is acceptable. All studies conducted to date indicate that the process will deliver finished product of suitable and reproducible quality. The in-process controls (IPCs) and defined process parameters are adequate for this type of manufacturing process and pharmaceutical form. IPCs are used to check post-granulation ribbon density and capsule fill weight.

Product specification

The finished product release specifications shown include appropriate tests for this kind of dosage form including appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, BHT content, and microbial enumeration.

The specification is compliant with ICH guidance and Ph. Eur. Requirements. Limits for the 2 specified degradation products are considered acceptable, considering that they are also metabolites. The justifications for not including tests for a process impurity, chiral purity, and water content are also considered acceptable.

The applicant has performed a risk assessment concerning potential elemental impurities in the finished product in accordance with ICH Q3D. Three batches of finished product were testing, demonstrating no elemental impurities present above 30% of their PDEs. The omission of a test for elemental impurities in the finished product is considered acceptable.

The initially submitted risk assessment for nitrosamine impurities was considered inadequate by the CHMP as it only covered the active substance and did not mention the use of stoichiometric sodium nitrite in the synthesis of one of the starting materials, resulting in a major objection. In response, the

applicant provided a more thorough risk assessment considering also finished product risk factors. The carry over of sodium nitrite into the active substance process was also addressed by testing for the present of small molecule nitrosamine derived from susceptible amines in the process using a suitably sensitive analytical method – no nitrosamines were detected. Therefore, it is considered acceptable not to include any specific measures for control of potential nitrosamine impurities.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 9 batches used in clinical and stability studies confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches and 3 clinical batches of finished product stored for up to 48 months under long term conditions (25ºC / 60% RH), for up to 36 months under intermediate conditions (30ºC / 75% RH), and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, degradation products, dissolution and microbial enumeration. The 2 specified oxidative degradation products increased to 1.3% after 48 months under long term conditions, 3% after 36 months under intermediate conditions, and 2% after 6 months under accelerated conditions. The increase is not of concern since both degradants are also metabolites. Dissolution was carried out with a previous method up to 42 months with no trends observed. However, when tested with the new method, dissolution rate decreased over time and was out of specification after 6 months under accelerated conditions.

In a photostability study, the capsules were exposed to light according to ICH Q1B. While a slight increase of sulfoxide degradation products was observed under ICH photostability conditions on the exposed product, the product in the container closure system was unchanged. This indicates that the HDPE bottle is suitable to protect the capsules from light and no additional light protection is needed.

In-use stability data was provided for two batches studied for 30 days. All results were found within specification with no observed changes. No specific in-use shelf-life is therefore needed or proposed.

Based on available stability data, the proposed shelf-life of 48 months in the HDPE bottles with the restriction "do not store above 30 ºC" as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture are provided.

No other excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The major objection relating to the dissolution specification was addressed by tightening the specification limits and adding a second timepoint. Nitrosamine concerns were mitigated by provision of a more thorough risk assessment and confirmatory testing data indicating that no nitrosamines were detected.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The PPAR family are ligand activated nuclear receptors which heterodimerise with the nuclear retinoid-X-receptor (RXR) and after interaction with a number of transcriptional co-activators binds to PPAR response elements of target genes. The PPAR family are major regulators of energy homeostasis and metabolic processes. The different subtypes of PPAR receptors have overlapping functions and tissue distribution, and in addition, the PPAR receptor density may vary in different tissues depending on a number of factors such as cell type and physiological/pathological conditions. In addition, the applicant concludes that since the PPAR activation profile of seladelpar is species-dependent, different biological effects may be observed in different species, particularly when comparing effects in rodent with those in non-rodents. This conclusion is supported and is considered in assessment of toxicological studies in different species.

In vitro studies have shown that seladelpar binds and activates PPARδ with the highest selectivity in human and in all investigated non-clinical species, followed by a lower affinity to PPARα and low or no affinity to PPARγ.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro

Biochemical assays: The crystal structure over binding characteristics of seladelpar and the active metabolite M2 (O-desethyl) to the human PPARδ ligand binding domain (LBD) was measured by 3 orthogonal biochemical methods. Seladelpar and M2 bind to PPARδ in a similar fashion. This was

consistent with biochemical characterisation of seladelpar and M2 binding affinity to PPARδ, where seladelpar was shown to bind with a 5- to 9- fold higher affinity in comparison to M2. In addition, seladelpar binding affinity to PPARα and PPARγ were analysed, and the affinity for PPARδ compared to PPARα and PPARγ, was ~ 418 and 230 higher, respectively. These data can be considered to provide convincing evidence of selectivity of seladelpar for PPARδ subtype. The M2 metabolite also demonstrated selectivity for PPARδ, though with less affinity than the parent.

Cell based assays: Seladelpar selectivity and potency was also assessed in cell-based reporter gene assays (GAL4) using human, rat, mouse, hamster, rabbit and monkey ligand binding domains of PPAR-α, δ, γ. Seladelpar activated human PPARδ with the highest selectivity and potency among the tested species and with a 630-fold higher potency for human PPARδ compared to human PPARα. The seladelpar EC50 values for activation of PPARδ in different species were the following: human 0.002 µM; Cynomolgus monkey 0.017 µM; rabbit 9.6 µM; rat 0.41 µM; mouse 0.12 µM. No substantial activity was observed on PPARδ in rabbit. Both seladelpar and M2 were highly selective for human PPARδ activation, with a 115-fold greater activation of seladelpar compared to M2. M2 had less potent PPARδ activity than seladelpar in all species, 224-fold lower than seladelpar in Cynomolgus monkey. The metabolite M1 and M3 had no relevant activity against human PPARs.

Based on these studies seladelpar is a potent PPARδ agonist in humans and monkeys but is considerably less potent against rat and mouse PPARδ. In rodents, and to a lesser extent in Cynomolgus monkeys, seladelpar also stimulates PPARα receptors but with almost no activity in humans.

An extensive analysis of the PPARα -, peroxisome proliferation - and PPARδ responsive genes to seladelpar and M2 activation was performed on mouse, rat, Cynomolgus monkey and human hepatocytes co-cultured with Kupfer cells. PPARα-responsive genes were upregulated by seladelpar and M2 at 10 µM in mouse, rat, and monkey cells, with a minor effect on human cells. The peroxisome proliferation responsive gene *Ehhadh* was induced 4-fold by seladelpar in mouse cells compared to DMSO exposed cells while equally low expression was found in rat, Cynomolgus monkey and human cells. Acox1 expression was increased 1.7-fold in human and ranged between 1.1-1.5-fold in Cynomolgus monkey, rat and mice, respectively.

Seladelpar's effects on endogenous bile acid content and expression of genes involved in bile acid transport/metabolism were assessed and compared to comparators involved in the processing of bile acids in sandwich cultured human hepatocytes (SCHH). Seladelpar reduced bile acids in media with >50%, and reduced CYP7A1 mRNA content dose-dependently with 31-80% below solvent control within the concentration range of 0.316-10 µM. CYP7A1 encodes for cholesterol 7-α hydroxylase, which catalyses the first step in bile acid synthesis.

In addition, the anti-inflammatory response by seladelpar was investigated in THP activated macrophages and was shown by reduction of pro-IL-1β mRNA levels induced by lipopolysaccharides (LPS) plus interferon gamma (IFNγ) by 85% and limited increases induced by cholesterol dose-dependently by up to 60%. The latter change was accompanied by a reduction of mature IL-1β polypeptide release by 66% following incubation with seladelpar.

In vivo

The pharmacodynamic response was investigated in CD-1 mice after oral administration of seladelpar via diet in two dose levels corresponding to 12.3 and 29.3 mg/kg/day for up to 6 days resulting in a plasma exposure of seladelpar greater than the mouse PPARδ Cell-EC_{50} for efficacy. In comparison to animals receiving control diet, the C4 levels in plasma decreased 3.5- and 4.8-fold for the respective dose level. Expression levels of CYP7A1 mRNA in the liver decreased with 77% and 56%, and PDK4 mRNA (considered to be mainly a PPARα response) were increased 13.8- and 450-fold for the low and high dose respectively. C4 levels in plasma of C57Bl/6 mice were also analysed after a single dose of

10 mg/kg and found to be reduced from 2 hours (C_{max}, 5.8 ng/mL) to 16 hours post-dosing. No effect was detected 24 hours after administration. These results demonstrate PPARδ pharmacodynamic effect by *in vivo* reduction in C4 plasma levels, reduction in hepatic bile acid synthesis and decreased CYP7A1 mRNA in liver following seladelpar exposure. In addition, PDK4 mRNA increased up to 450-fold compared to control diet which is indicative of a strong PPARα response in livers from mice fed a seladelpar containing diet.

In two other studies the effect on seladelpar on intestinal absorption of cholesterol was investigated in mice at a gavage dose of 10 mg/kg/day or in an admix to diet at an approximate dose level of 15 mg/kg/day. The result showed a dose-dependent reduction in cholesterol absorption versus control (-29.4% and -45%, respectively) by seladelpar.

The effect of seladelpar in a carbon tetrachloride (CCl4) model of liver fibrosis in mice was investigated. After 5 weeks CCl4 treatment, a dose of 10 mg/kg of seladelpar (or vehicle) was introduced in parallel with CCl4 treatment for another 3 weeks. Seladelpar treatment reduced collagen deposits and decreased the density of EC matrix in liver compared to vehicle treated mice. Moreover, the CCl4-treated mice that were co-administrated with seladelpar for the last three weeks of treatment, had less collagen deposits than mice sacrificed directly after 5 weeks treatment with only CCl4. In addition, seladelpar increased liver weights due to PPARα-agonism. Hepatomegaly is a rodent effect of seladelpar, which is not seen in humans. This is well-known phenomenon and largely reported in scientific literature.

Activation of PPARδ and PPARα responsive genes by seladelpar was investigated in wt mice and in PPARα knockout mice in an oral 14-day study at seladelpar doses of 3 and 20 mg/kg/day. Seladelpar was shown to activate PPARα and PPARδ in C57Bl/6N wild-type mice and only PPARδ in the PPARα-knockout mice at the same exposure levels as in the 2-year carcinogenicity study. This suggests that the exposure levels are sufficient for evaluation of toxicity *in vivo* in mice.

Based on these studies pharmacodynamic activity was shown in mouse and rats when PPARδ responsive gene expression were analysed in livers after two weeks seladelpar treatment. The gene expression raised already at a dose level of 3 mg/kg/day. Moreover, pharmacodynamic activity was observed in *in vivo*-studies on mice from both single- and repeated doses of 10 mg/kg/day seladelpar.

2.5.2.2. Secondary pharmacodynamic studies

The off-target activity of seladelpar was investigated against a panel of 48 receptors, transporters, and ion channels for evaluation of EC_{50} values, and in a panel of 15 nuclear and 1 non-nuclear human receptor. The inhibition by seladelpar was <50% at 10 µM for all investigated targets with the exception of the [Cl-]-channels. After further investigation using cerebral brain homogenates, the IC_{50} for seladelpar binding at the Cl- channel was 10 µM with a K_i of 8.5 µM. An off-target activity by seladelpar is not likely at therapeutic plasma concentrations. Comparing to clinical C_{max} of 350 nM for total drug and 3.5 nM for free drug the calculated *in vitro* IC_{50} and K_i are without clinical relevance.

The off-target activity of the metabolites, M1, M2, and M3, have not been completely addressed in the panel but appears to be covered in the toxicological studies.

A number of studies regarding pharmacological effects involving energy metabolism and blood lipids (cholesterols, triglycerides and free fatty acids) were presented in the secondary pharmacology section with various specie-dependent effects on blood lipid levels. Chronic seladelpar administration was investigated in cynomolgus monkeys with the purpose to assess muscle energy metabolism by tissue metabolomics and serum levels of creatinine and creatine. After 43 and 78 days of seladelpar treatment, serum creatine concentrations were approximately 1.7-fold and 2.3-fold higher compared

with the vehicle-treated group. Metabolic effects were also studied in mice and guineapigs fed a high fat diet. Seladelpar treatment resulted in reduced weight gain and prevented lipid increases in serum, without an effect on food intake.

2.5.2.3. Safety pharmacology programme

The safety pharmacology of seladelpar was evaluated in a number of *in vitro* and *in vivo* studies.

The CNS and neurobehavioral safety pharmacology of seladelpar was evaluated in male Sprague Dawley rats by a modified Irwin screen, at PO dose levels of 250, 500, or 1000 mg/kg. No mortality or effects on body weight or temperature were recorded. The only clinical observation was decreased faecal output for all animals at 1000 mg/kg. No treatment-related neurobehavioral signs were observed in male rats up to 1000 mg/kg.

In vivo cardiovascular and respiratory safety pharmacology of seladelpar was conducted in one GLP-compliant study in male- and in one non-GLP study in female Beagle dogs. No effects on cardiovascular and pulmonary parameters or metabolic blood changes were observed in female anesthetised dogs up to a cumulative seladelpar plasma concentration of 59250 ng/mL or the cardiovascular and pulmonary parameters in unrestrained conscious male dogs up to the highest dose level of 80 mg/kg with a seladelpar and M2 plasma concentrations of 125225 ng/mL 2528 ng/mL, respectively. Cardiovascular safety was also assessed in Cynomolgus monkey in the 52-week repeated dose toxicity study and no effects of seladelpar were detected on any of the measured ECG parameters. A non-GLP study in anesthetised guinea pigs receiving increased IV doses in a similar manner as the non-GLP study in female Beagle dogs were conducted, also without any cardiovascular concerns up to a cumulative dose level of 10 mg/kg. No *in vitro* affinity or potency studies have been presented in the primary pharmacology section to assess the relevance of dog for the cardiovascular and respiratory studies which is a deficiency. However, in light of clinical data and that no cardiovascular effects including ECG anomalies has been detected in the 52-week repeat dose toxicity study on Cynomolgus monkey, this limitation is not pursued.

The inhibition of hERG was assessed for seladelpar up 3 µM showing an inhibition of 7.7%. The margin based on the free drug concentration of 3.5 nM in human, is x857. An hERG inhibition by seladelpar is thus unlikely. The human major metabolites have not been investigated for hERG inhibition, however, since no signs of QT-prolongation was observed in clinical trials, the likelihood of metabolite-mediated hERG inhibition appears unlikely.

2.5.2.4. Pharmacodynamic drug interactions

Specific nonclinical pharmacodynamics drug interactions studies have not been performed with seladelpar. All seladelpar studies for treatment of PBC were in combination with UDCA, based on the pharmacodynamics/ efficacy rationale for the combination. The mechanisms of seladelpar and UDCA are complementary in the treatment of PBC. This rationale is acceptable, and no nonclinical pharmacodynamics drug interactions studies are deemed to be necessary.

2.5.3. Pharmacokinetics

Analytical methods
Analytical methods were developed and validated to quantify the concentration and stability of seladelpar in appropriate dose formulations for *in vitro* and *in vivo* studies.

Validated LC-MS/MS bioanalytical methods were developed for quantitation of seladelpar and selected metabolites in mouse, rat, rabbit, dog, and monkey plasma to support GLP TK studies. Qualified and partially validated methods were developed to support single dose, dose-range finding and pilot studies.

In early toxicology studies in the mouse, rat, monkey, and dog, inappropriate bioanalytical data manipulation was discovered after the studies were finalised. Affected methods validations were successfully repeated, and data impacted by the original validation were considered usable (e.g. parent seladelpar). Data which were compromised due to inappropriate practices in sample analysis were excluded from presentation in the written and tabulated summaries and footnoted as such were appropriate.

Absorption

The PK data was collected from single dosing in mouse, rat, dog, and monkey after IV and oral administration. The TK data was collected from once daily oral administration up to 104 weeks in mouse and rat, developmental toxicity studies in rabbit, up to 4 weeks in dogs and up to 52-weeks in monkey.

After single oral administration, seladelpar was rapidly absorbed in mice, rats, dogs and monkeys, with oral bioavailability greater than 69% in all species evaluated. Following repeated oral administration, absorption was rapid with mean time to maximal concentration values generally within the first few hours after dosing. The terminal phase t½ varied between species, ranging from 1 to 11 hours in mice, 2 to 15 hours in rats, 5 to 47 hours in dogs and 4 to 43 hours in monkeys. Terminal t½ values tended to increase with dose, reflecting an increasingly longer time span over which the slopes could be determined, whereas the highest t½ values reported for dogs and monkeys generally represented one group of animals in a TK analysis, and could be attributed in part to inter-animal variability in disposition. Systemic exposure (AUC) to seladelpar increased in a dose-dependent manner; however, exposures significantly decreased after repeated daily dosing in rats and monkeys, suggestive of possible autoinduction leading to increased metabolism of seladelpar over time. There was evidence of accumulation after repeated daily dosing in mice and dogs. The exposure of seladelpar was generally higher in female mice and rats, while there were no significant differences in seladelpar TK between sexes in dogs or monkeys.

Distribution

Seladelpar and M2 (seladelpar metabolite) were extensively protein bound (≥ 99.5%) in plasma from mice, rats, rabbits, dogs, monkeys, and humans in a concentration independent manner from 200 to 20,000 ng/mL. M2 binding was generally less than parent, ranging from 98.9% to 99.4%. Seladelpar is preferentially bound to human serum albumin as compared with alpha 1-acid glycoprotein (AAG).

Seladelpar was widely distributed with volumes of distribution greater than the volume of total body water observed in rats and monkeys and approximately equal to total body water in mice and dogs.

A quantitative whole-body autoradiography (QWBA) study was performed in albino SD rats administered a single 15 mg/kg (200 µCi/kg) oral dose of [^{14}C]-seladelpar. The results indicated that seladelpar-derived radioactivity was widely distributed in both sexes after oral administration. The tissues with the highest radioactivity across most time points were in the gastrointestinal tract (including stomach and small and large intestine), liver, kidney, bladder, and lung. Radioactivity was not measurable in bone, eye, muscle, pancreas, fat (white), cerebellum, cerebrum, thyroid, mesenteric lymph nodes, prostate (males), testes (males) and uterus., In general, at 24 hours after dosing, very little radioactivity was detected systemically; radioactivity was detectable in only 1 (female) or 3 (male) tissues at 72 hours and in no tissues in either sex at 168 hours.

Another QWBA study in pigmented Long Evans rats also showed wide distribution of radioactivity in both sexes after a single oral dose. As with albino animals, tissues with the highest radioactivity included liver, kidney (including renal cortex and medulla), lungs, and oesophagus. Radioactivity was not detected in any tissues in males and females by 168 hours after dosing, except for adrenal gland in females, which reached the limit of detection between 336- and 672-hours after dosing. This indicates complete elimination of seladelpar from the body. Tissue distribution patterns were similar between male and female animals, and there was no apparent evidence of melanin binding.

Metabolism

Seladelpar is primarily metabolised by CYP enzymes across all species. In *in vitro* studies, seladelpar was significantly converted (partly non enzymatically) to a sulfoxide metabolite (M1 or JNJ-27438190) in rat, monkey, and human S9 fractions and HLM and this was more pronounced in the dog. Unchanged parent drug accounted for 20% to 35% of the S9 and HLM samples at 90 minutes. Loss of the O-ethyl moiety by O-dealkylation of seladelpar to form M2 (or JNJ-27554098) was a major metabolic pathway in the rat and human and was minor in dog and monkey. The O-desethyl + sulfoxide metabolite (M3 or JNJ-27554111) was found at low levels in rat, monkey, and human and at trace levels in dog. Hydroxylated + sulfoxide seladelpar (M5) was a minor metabolite observed in all species. Other minor metabolites were observed. Overall, the metabolic profile was qualitatively similar across species in S9 fractions and HLM, and there were no unique human metabolites observed.

Three major metabolites were found circulating in plasma, with the O de-ethylated (M2) metabolite being the most predominant in most species. M1 and M3 levels were less than that of seladelpar while M2 was lower than seladelpar in monkeys and significantly greater than seladelpar in mice and rats. Additional circulating metabolites were observed in dedicated metabolism studies, particularly in monkeys; however, none were deemed to be major metabolites in humans according to MIST regulatory criteria and were not evaluated further in the programme. Metabolite profiling in plasma of humans receiving a single dose 14C-labeled seladelpar demonstrated that M1, M2, and M3 were all present at levels ≥ 10% of total plasma radioactivity. Thus, M1, M2, and M3 are considered major metabolites according to MIST criteria. All 3 metabolites were observed in the circulation of the toxicology species.

M2 was shown to be an active metabolite with potency 22 to 175 times lower than that of seladelpar against rat and human PPARδ *in vitro*, respectively, whereas M1 and M3 showed no appreciable activity in *in vitro* pharmacology models.

Samples from the QWBA study performed in albino SD rats were used for metabolite profiling. Seladelpar appeared to be extensively metabolised by the rat *in vivo*. Approximately 20 metabolites were observed in urine, 14 in feces, 21 in bile, and 8 in plasma. Unchanged parent drug was observed in feces, bile, and plasma, but not in the urine. Significant biliary excretion was recorded in both sexes. The predominant metabolites were products of S-oxidation (M1), dealkylation (M2), and phase II conjugation. In plasma, the major metabolite was M2, comprising approximately half of the radioactivity in the sample, with M1 and M3 comprising approximately 5% and 3% of radioactivity in the sample, respectively.

The metabolism of seladelpar was characterised in *in vivo* samples from rats and dogs administered 20 mg/kg and 10 mg/kg seladelpar p.o., respectively. Urine and fecal samples were collected up to 24 hours after dosing. Plasma samples were pooled from 1 to 4 hours for rat and 1 to 6 hours for dogs. Unchanged seladelpar and the metabolites, M1 and M2 were the only drug related materials identified in both the rat and the dog. Unchanged seladelpar was the major circulatory drug component in both rats (males: 63% and females: 67%) and dogs (males: 98% and females 96%). Seladelpar accounted for 27.6% and M1 72.4% of the urine sample in male dogs, whereas in females M1 accounted for 97.5%. In dog faeces, seladelpar was present for 24.5% in males and 33.8% in females, M1 64.5%

(M) and 59.3% (F) and M2 as 6.4% (M) and 5.9% (F). The results suggest that dealkylation is the major metabolic pathway in rats and S-oxidation in dogs. Overall, there were no obvious sex differences observed for either species.

Samples were obtained from toxicology studies and from Clinical Study 800025-NAP-1001 in order to characterise the metabolism of seladelpar in monkeys and humans. Plasma samples were pooled from 1 to 8 hours for monkeys and 0.5 to 3 hours for humans. Urine samples were pooled from 0 to 24 hours for monkeys and 0 to 96 hours for humans. In monkeys, unchanged seladelpar was the major circulatory drug-related component (males 53% and females 19%). The sulfoxide metabolite (M1) and the O-desethylated metabolite (M2) were present at 24% and 17% in males and 20% and 15% in females, respectively. In human plasma, unchanged seladelpar, M1, and M2 were the major circulatory components, accounting for 48%, 37%, and 14% of the sample, respectively. Metabolites M3 (O-desethyl sulfoxide), M6 (hydroxy desethyl) and M15 (O-glucuronide of M2) were identified in trace amounts. In human unhydrolyzed pooled urine samples, seladelpar was less than 1% of sample while the major metabolites detected were M1, M2, M3, M6, M8 (sulfone), and M10 (O-desethyl sulfone). M1 and M5 were observed in trace amounts. The glucuronide metabolites (M11-M15) were identified in amounts ranging from trace to 8.8% of sample. After glucuronidase treatment of the urine samples, seladelpar increased to 5% of the sample, M1 to 28%, M2 to 15%, M3 to 30%, M8 to 4%, and M10 to 18% of the sample, respectively.

In a human [^{14}C]-seladelpar mass balance study metabolite profiles and metabolite identification of [14C]-seladelpar-related radioactivity were determined in plasma, urine, and feces samples collected from female and male human subjects after a single oral dose of 10 mg [14C]- seladelpar. Plasma samples were pooled across subjects for each sex at 0.25, 1, 2, 4, 8, 12, 16, 24, 36-, 48-, 96-, and 144-hours post-dose to produce inter-subject, sex-specific, time-point pools. Radioactivity in the processed samples was profiled by HPLC with radiochemical detection and metabolites were identified by chromatography with a known standard and by LC-MS/MS methods. Seladelpar underwent extensive metabolism in human subjects to produce 13 identified/characterised metabolites.

Circulating metabolites in humans that accounted for ≥ 10% of total plasma radioactivity were M1, M2, and M3. All these entities were observed in plasma of at least one of the toxicology species.

Excretion

Tissue distribution, metabolism, and excretion of seladelpar was determined in male and female Sprague-Dawley rats after administration of a single 15 mg/kg (200 µCi/kg) oral dose of [^{14}C]-seladelpar. The total recovery of the radioactive dose of seladelpar was > 90% in intact rats, with the majority excreted in feces. Fecal excretion was the main route of elimination of administered radioactivity, with recovery of 87% and 64% of dose in male and female rats, respectively. A total of 90% of the total dose eliminated in feces was recovered within 48 hours after dosing. Urinary excretion of administered radioactivity was lower in male rats, with 4% of administered dose recovered compared with 25%, in female rats. At 168 hours after dosing, the radioactivity in carcasses was 0.2% and in cage washes 1% to 2% of total radioactivity. Biliary excretion was significant in rats, with total radioactivity recovery values of 89% and 87% in males and females, respectively, through 72 hours after dosing.

Radioactivity is primarily excreted in the form of M2 with 62% and 55% of dose in the combined excreta of males and females, respectively. In males, metabolite M2 appears mostly in the feces, with only trace amounts observed in the urine. In females significantly more (12.6%) of the dose appears in the urine over 24 hours as metabolite M2. The remaining metabolites in the excreta of both sexes comprise less than 5% of the dose. Parent [14C]-seladelpar at 0-24 hours accounts for only relatively small amounts of the total administered dose of radioactivity (7.7% and 2.9% thru 72 hours post-dose in males and females, respectively).

In contrast, in humans, urinary excretion was the major route of elimination for total radioactivity (Study No. CB8025-11734). Mean urinary recovery of total radioactivity was 73.4% of the dose, and mean fecal recovery was 19.5%. Less than 0.01% of dose was excreted in urine as unchanged seladelpar. The percentage of seladelpar dose excreted in urine as metabolites was 8.3% for M1, 1.2% for M2, and 27.5% for M3. Metabolite M2 accounted for 11% of dose in feces. Seladelpar and all other metabolites identified in feces were minor, accounting for <10% of the total dose.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Two GLP-compliant oral gavage and intraperitoneal (ip) administration single-dose toxicity studies in mice and rats were conducted. Following an oral single dose, seladelpar was well tolerated at up to 1000 mg/kg in mice, and up to 250 mg/kg in rats. In mice, no clinical signs were observed at up to 1000 mg/kg. In rats, a single dose of seladelpar at ≥500 mg/kg was associated with dose-dependent clinical signs including decreased activity, ataxia, ptosis, hunched posture and cold to touch, and observations of distended stomach, discoloured GI tract and/or stomach pyloric region.

2.5.4.2. Repeat dose toxicity

Repeat-dose po administration of seladelpar was evaluated at up to 13 weeks in CD-1 mice, up to 26 weeks in Sprague-Dawley rats, up to 4 weeks in dogs, and up to 52 weeks in cynomolgus monkeys. Most of the repeat-dose studies were GLP-compliant. In addition, one supporting 8-week study using oral and subcutaneous dosing was performed in rats (non-GLP).

Target organs identified in the repeat-dose study package include liver in mouse, rat, and monkey; skeletal muscle in mouse, rat, and monkey; cardiac muscle in rats; and the adrenal gland in rats and monkeys; and effects haematology in mouse, rat, dog and monkey. After chronic administration, rats also showed changes in white adipose tissue, oesophagus, and kidneys. In dogs in the 28-day study, target organs included bone marrow, skeletal muscle, testis, and thymus, and at 50 mg/kg/day, prostate and lymph nodes (mesenteric and popliteal).

Clinical signs, body weights and associated findings

Throughout the repeat-dose studies, there were in general few clinical signs noted, but in dogs and monkeys, emesis and feces effects were observed (in dogs, no or reduced feces, and watery stool in monkeys). Hunched appearance and decreased activity were also recorded in monkeys.

In rats, dogs and monkeys, dose-limiting toxicity involve marked body weight loss associated with pronounced effects on food consumption. These adverse effects caused termination of several animals.

In the dog 4-week study, two males at 50 mg/kg/day were for terminated for welfare reasons due to marked reduction in body weight associated with no food consumption. In monkeys, four animals were euthanised in a poor condition due to body weight loss; one male at 100 mg/kg/day in the 4-week study, one female at 50 mg/kg/day in the 13-week study, and one female at 25/12.5/8 mg/kg/day and one male at 25/12.5 mg/kg/day in the 52-week study. Microscopic findings in these animals were generally similar to that of animals surviving to scheduled termination. There were also marked effects on body weight and food consumption in rats. In the 13-week study, one female each at 50 and 80 mg/kg/day were found dead. In the absence of the cause of deaths, they are considered treatment related.

In the 14-day non-GLP mouse study, mortality occurred in males at 400 mg/kg/day and in females at doses ≥200 mg/kg/day. Twelve main study animals were found dead (2 males and 7 females at 400 mg/kg/day and 3 females at 200 mg/kg/day) and 3 were euthanised early (2 males and 1 female at 400 mg/kg/day) between Days 9 and 15 of the study. The early decedents were noted to be dehydrated, weak, cold to touch, have decreased activity and respiratory rate, and/or tremors before death. A slight increase in mean body weight was observed and considered likely related to liver enlargement and corresponding abdominal distention. In the 13-week mouse study, an increased body weight was observed in females at 50 mg/kg/day.

In the rat 26-week study, minimal to mild adipocyte atrophy in white adipose tissue was observed in male rats at 50 mg/kg/day and in subcutis adipocyte atrophy in males at ≥5 mg/kg/day and female rats at 80 mg/kg/day. The adipocyte atrophy was considered a reflection of the marked effects on body weights (≥15 mg/kg/day). In addition, minimal to mild decreased zymogen in pancreas was present in rats at 50/80 mg/kg/day. Decreased pancreatic zymogen can occur secondary to decreased food consumption with concomitantly decreased body weight. However, the relationship of decreased pancreatic zymogen to weight loss in the absence of decreased food consumption is not known.

In pancreas, a reversible minimal to mild decrease in zymogen was observed in the 26-week at 50/80 mg/kg/day and in the monkey 52-week study at ≥5 mg/kg/day. The finding may be secondary to decreased food consumption with concomitantly decreased body weight.

Liver and bile duct (mice, rats and monkeys)

Dose-related increases in liver weight accompanied by hepatocellular hypertrophy, necrosis and elevations of ALT and AST. 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 NOAEL was 1 mg/kg/day for males and 5 mg/kg/day in females due to adverse hepatocellular necrosis at higher doses, corresponding to exposure margins 2.2- and 11-fold, respectively, over the human AUC (1095 ng·h/mL) at the 10 mg/day clinical dose.

In the mouse 13-week study, minimal and reversible bile duct hyperplasia was observed in 1/10 males and in 3/10 females at 50 mg/kg/day. Minimal and reversible bile duct hyperplasia was also observed in the rat 13-week study, in 5/10 males at 80 mg/kg/day. This finding was also present in the 52-week monkey study, in one male each at 1 and 5 mg/kg/day, but not at 25/12.5 mg/kg/day, and in 2 females each at 5 and 25/12.5/8 mg/kg/day. The latter female monkey was terminated for ethical reasons. The finding was still observed in one male at the end of the 8-week recovery period, indicating partial reversibility. There were no associated lesions such as inflammation, fibrosis, or bile duct dilation or neoplastic findings in bile ducts in the mouse or rat 2-year studies.

Bone marrow, spleen and red blood cell parameters (mice, rats, dogs and monkeys)

Dose-related reductions in red blood cell mass (red blood cells, haemoglobin and 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. The effects were generally reversible.

In mice, the effects on red cell mass were observed at ≥100 mg/kg/day after 14 days of dosing but were not observed after 13 weeks at doses up to 50 mg/kg/day. In the 4-week study in rats, decreased red blood cell mass at 100 mg/kg/day correlated with minimally increased extramedullary haematopoiesis observed in the spleen of male rats given ≥10 mg/kg/day, characterised by an

increase in the number of RBC precursors in the red pulp of the spleen, and this was indicative of a regenerative response. Similar minimal changes occurred in red cell mass at ≥50 mg/kg/day in the rat 13-week study and at ≥15 mg/kg/day in the rat 26- week study with no histologic correlates.

In the 4-week study in dogs, decreased reticulocyte counts and red cell mass parameters at 50 mg/kg/day correlated with decreased hematopoietic cells in the bone marrow at ≥5 mg/kg/day in males and at 50 mg/kg/day in females, particularly in the erythroid series. After a 4-week recovery period, the mean reticulocyte count was improved, red cell mass values were comparable to controls, and bone marrow was normal.

In the 4-week study in monkey, decreased erythropoiesis occurred, which was correlated with erythroid hypoplasia noted in bone marrow smears at 10 and 100 mg/kg/day, as well as observations of sternal bone marrow hypocellularity at 100 mg/kg/day in males, characterised by decreased numbers of myeloid and erythroid hematopoietic cells. Red blood cell mass was improved after a 4-week recovery period, but values had not yet returned to baseline and low reticulocyte counts and abnormal red cell morphology persisted, indicating persistence of decreased erythropoiesis and/or haemolysis. Bone marrow hypocellularity was not observed after the recovery period. In the monkey 13-week study, mild changes in red cell mass occurred at 50 mg/kg/day with no histologic correlates, and there were no definitive treatment-related effects on haematology parameters in the 52-week monkey study at up to the highest dose of 25/12.5 mg/kg/day in males and 25/12.5/8 mg/kg/day in females.

Kidney (mice, rats and monkeys)

Dose-related increases in kidney weight was observed in all repeat-dose studies in mice, rats and monkeys, but not in dogs. With a few exceptions at high doses, there were no microscopic correlates or findings in urinalysis. In the 14-day non-GLP mouse study, renal single cell necrosis was observed at doses ≥100 mg/kg/day. In the 14-day non-GLP monkey study, minimal to mild degeneration in the tubules of the cortex, accompanied by evidence of regeneration were observed in 2 males at the highest dose of 200 mg/kg/day. Finally, in the 26-week rat study, minimal hyperplasia of tubular epithelium was observed in males at ≥15 mg/kg/day and in females at 80 mg/kg/day and chronic progressive nephropathy in females at ≥15 mg/kg/day.

Skeletal muscle (mice, rats and monkeys)

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 was no skeletal muscle degeneration observed in the monkey 52-week study when tested up to Week 52 AUCs of at least 35- and 24-fold in males and females, respectively, the clinical seladelpar AUC (dose levels were lowered several times during the study). Ultrastructural analysis showed increased lipid vacuoles and increased mitochondrial size in skeletal muscle from the 26-week rat study at ≥15 mg/kg/day and increased mitochondrial size in skeletal muscle the 52-week monkey study at ≥1 mg/kg/day.

Adrenal gland (rats and monkeys)

In rats, minimal to slight cortex vacuolation of the zona glomerulosa (80 mg/kg/day) was observed following 13 weeks, and minimal to mild zona glomerulosa hypertrophy (≥5 mg/kg/day), minimal to mild zona fasciculata vacuolation (≥15 mg/kg/day) following 26 weeks of seladelpar administration. In monkeys, minimal to mild hypertrophy of cells in the zona fasciculata (≥5 mg/kg/day) was observed following 13 weeks but not after 52 weeks. Increased adrenal weigh was observed in dogs after 4 weeks, but with no associated microscopic alterations. The adrenal gland findings were fully reversible in the 13-week rat study and showed a partial resolution in the rat 26-week and in the monkey 13-week studies.

Thyroid gland (rat)

Minimal follicular cell hypertrophy was observed in all rat studies (4, 13 and 26 weeks) but not in other species. The finding was either fully or partially reversible following recovery. The severity of the finding did not increase by longer dosing duration. In the 13-week rat study, the hypertrophy was associated with significant decreases in mean T4 values in males at ≥10 mg/kg/day but no apparent changes in TSH values were observed.

Cardiac muscle (rat)

Minimal to slight cardiac muscle degeneration and/or necrosis 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. The findings were reversible in the 13-week study but not in the 26-week study. In the 2-year rat 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.

Oesophagus and non-glandular stomach (rats)

Epithelial hyperkeratosis of the non-glandular stomach and oesophagus was observed in rats following 14 days to 26 weeks repeated administration.

Urinary bladder (monkey)

In the monkey 52-week study, minimal to mild reversible cytoplasmic vacuolisation of the urinary bladder epithelium was observed in some animals at ≥1 mg/kg/day.

Male reproductive organs (dogs)

In dogs only, adverse effects were seen in male reproductive organs. In the 14-day non-GLP study, mild testicular degeneration was observed in the one male animal evaluated at 100 mg/kg/day, but not at 1 or 10 mg/kg/day. This male had lost 1.6 kg body weight during the dosing period. In the 4-week study, minimal to moderate degeneration of the seminiferous tubules of the testis was seen at 5 (2/3 dogs) and 50 mg/kg/kg (5/5 dogs). Additionally, at 50 mg/kg/day, interstitial cell atrophy was seen in all male dogs, and atrophy of the prostate gland was seen in 3/5 dogs. The reversibility of the testicular changes could not be evaluated due to the early euthanasia of the high dose male recovery animals. The testicular seminiferous tubule degeneration and prostatic atrophy may have been related to the testicular interstitial cell atrophy since the interstitial cells secrete testosterone, which is needed for spermatogenesis and prostate stimulation.

In a supportive 8-week rat study comparing po and sc administration routes, seladelpar initiated local reactions at the injection site such as scabs, sores and/or thickening of skin (macroscopic findings) and crusts, ulcers, skeletal muscle degeneration/necrosis, haemorrhage or inflammation (microscopic findings), when administered by sc injection for 8 weeks in rats. The initiation of local reactions by seladelpar after sc injection led to early termination of the study. The observed GI-tract effects were numerically higher after oral administration in comparison to sc administration.

2.5.4.3. Genotoxicity

Seladelpar was tested in a complete package of GLP genotoxicity studies in agreement with ICH S2(R1) guidance. The GLP-compliant Ames test showed negative results suggesting that seladelpar has no potential to induce mutations in the test system. Growth inhibition was observed in all tested

strains with highest concentrations of seladelpar. The GLP compliant L5178Y $Tk^{+/-}$ mouse lymphoma forward mutation assay showed cytotoxicity for seladelpar and therefore some of the tested cultures were discarded. A small increase in mutant frequency was recorded when treated with S9, however, no dose-dependence was observed and therefore this was not considered as a positive response. The *in vitro* genotoxicity testing is considered acceptable, and the interpretation of the results is agreed with.

In the mouse bone marrow micronucleus assay *in vivo*, results were negative following a single oral dose up to the dose limit of 2000 mg/kg of seladelpar. Analysis of seladelpar plasma concentrations indicate that seladelpar plasma exposures of up to about 186000 ng/mL, respectively, were reached in the study corresponding to ~1200-fold the clinical seladelpar C_{max} exposure. However, no bioanalysis validation report is found in the dossier, and it is noted that the plasma samples for bioanalysis were taken in heparin-coated tubes, while most other validations were performed with K_2EDTA tubes. Despite these deficiencies, it can be assumed that seladelpar was adequately evaluated within the study based on extrapolation to a study in the same mouse strain with reliable bioanalysis/TK data. Day 1 TK data from the 13-week mouse study resulted in seladelpar C_{max} exposures in male/female mice of 32033/35067 ng/mL following a dose of 50 mg/kg. This exposure is >200-fold above the clinical C_{max} of 155 ng/mL. Thus, a dose of 2000 mg/kg likely result in higher exposure.

There is no mention in the documentation on the genotoxicity of the major metabolites M1, M2 and M3. However, metabolites M1, M2 and M3 are formed in rat S9 and are therefore considered evaluated within the seladelpar *in vitro* studies.

Metabolite M2 is a major metabolite that exceeds seladelpar C_{max} and AUC exposure by about 1.5 and 3-fold, respectively, in humans. The exposure to M2 was analysed in the *in vivo* micronucleus test and showed plasma concentrations of up to 216000 ng/mL, corresponding to 911-fold the clinical M2 C_{max} exposure. Although it is unclear if the exposure data are reliable (see above) it seems reasonable to assume that M2 was adequately evaluated in the *in vivo* study. As example, in the mouse carcinogenicity study, Week 26 M2 C_{max} in male/female mice was 4520/4290 ng/mL (~18-fold the clinical M2 C_{max}) following the high dose of 20 mg/kg/day. A dose of 2000 mg/kg likely result in higher exposure.

Exposure of metabolites M1 and M3 was not analysed in the *in vivo* micronucleus test. In the 13-week mouse study report, same strain as used in the micronucleus test, the bioanalysis/TK for M1 and M3 were removed as data was not considered reliable. Finally, in the carcinogenicity study, M1 and M3 were analysed by a non-validated method showing Week 26 C_{max} exposures of 814/1040 (M/F) and 170/166 (M/F), for M1 and M3, respectively, following a dose of 20 mg/kg/day, corresponding to about 24- and 3.8-fold, the clinical metabolite C_{max}.

Metabolites M1, M2 and M3 have been evaluated for genotoxicity *in vitro* and *in vivo* and are considered as negative for genotoxic potential.

2.5.4.4. Carcinogenicity

The carcinogenicity of seladelpar was evaluated in 2-year studies in mice and rats at AUC exposures up to 82-fold (male mice), 115-fold (female mice), 22-fold (female rats) and 65-fold (male rats), relative to the clinical daily dose of 10 mg/day. In addition, mechanistic studies were conducted to support a MoA for the observed liver tumours.

In the mouse study, dosing of 0, 5, 10 and 20 mg/kg/day was selected. The high dose male group showed higher mortality from week 80 of the dosing phase, and dosing was suspended during week 96 as the number of surviving male mice had reached 20 animals. During week 102, the remaining males in the 20 mg/kg/day group were sacrificed as the number of surviving animals was 15. At terminal

necropsy during week 105, numbers of live male animals / group were 29 (control), 33 (5 mg/kg/day) and 28 (10 mg/kg/day). Dosing of female mice groups 10 and 20 mg/kg/day was suspended after week 101 as the number of surviving female mice had reached 20 animals. The numbers of live female mice / group at the terminal necropsy during week 105 were 20 (control), 24 (5 mg/kg/day), 19 (10 mg/kg/day) and 19 (20 mg/kg/day). Based on the results, male mice were more sensitive to seladelpar toxicity, however, the reason for sensitivity is unclear.

Dose-dependent, non- or pre-neoplastic findings were observed in liver and bile duct (increased incidence and/or severity of hepatocellular hypertrophy/hypereosinophilia and pigment, increased inflammation, individual cell necrosis, basophilic foci and oval cell and bile duct hyperplasia), in non-glandular stomach (hyperkeratosis) and in eye (lens cataracts) of males and females. In males only, findings were also seen in glandular stomach (increased severity of epithelial hyperplasia), in lacrimal gland (inflammation/degeneration) and in seminiferous tubules (bilateral atrophy/degeneration).

Neoplasms considered treatment-related were observed in liver and in non-glandular stomach.

Hepatocellular adenoma/carcinoma was observed in 9 (14%), 22 (34%), 27 (42%) and 33 (51%) males at 0, 5, 10 and 20 mg/kg/day, respectively, and in 2 (3.1%), 3 (4.6%), 7 (11%) and 9 (14%) females at 0, 5, 10 and 20 mg/kg/day, respectively. Incidence rates were significantly increased for all three treated male groups and for females given 10 or 20 mg/kg/day groups.

Squamous cell carcinoma in the non-glandular stomach was observed in one male each given 5 or 10 mg/kg/day, one female given 5 mg/kg/day, four females given 10 mg/kg/day, and two females given 20 mg/kg/day and was the cause of death in nearly all of the affected animals. Although no squamous cell neoplasms were present in males at 20 mg/kg/day, moderate hyperplasia was present in one male at 20 mg/kg/day and may have represented a pre-neoplastic finding. Although the incidence of this finding in dosed groups was low and did not show statistical significance (with the exception of females given 10 mg/kg/day), squamous cell carcinoma of the non-glandular stomach is considered a rare spontaneous neoplasm (Maekawa et al., 1996), and the occurrence in this finding in only seladelpar-treated groups was considered test article-related by the Study Director.

Of uncertain relation to treatment were benign epithelial ovarian neoplasms observed in mice. These neoplasms (adenoma, cystadenoma and tubulostromal adenoma) were observed in 2 (3.1%), 7 (11%), 8 (12%) and 3 (4.6%) females at 0, 5, 10 and 20 mg/kg/day, respectively. Although no dose-response is evident, it is noted in the study report that the incidences at 5 and 10 mg/kg/day are considered high compared with published data.

A NOEL for carcinogenicity was not determined in the mouse study and is less than 5 mg/kg/day in both males and females (AUC_{0-24} 5740/16700 ng*h/mL in M/F), corresponding to AUC margins lower than 5/15-fold (M/F) the clinical AUC.

In the rat study, dosing of 0, 3, 10 and 30 mg/kg/day was selected. The high dose group dosing was discontinued during weeks 91 (females) and 93 (males), during week 97 for control females as well as for 3 and 10 mg/kg/day females: during week 96 for 30 mg/kg/day females and during week 102 for all surviving male rats. At sacrifice, survival for males was 19 (control), 26 (3 mg/kg/day), 23 (10 mg/kg/day) and 14 (30 mg/kg/day) and survival for females was 20 (control), 20 (3 mg/kg/day), 20 (10 mg/kg/day) and 15 (30 mg/kg/day). The mortality was increased with high dosing with no observed sex difference.

Dose-dependent body weight decrease was recorded in males and significant decrease in females receiving high dose 30 mg/kg/day. As an increase in the mean food consumption was recorded, it was suggested that the decrease in body weight was due to increased metabolic activity caused by seladelpar.

Dose-dependent, non-neoplastic findings were observed in the lungs (alveolar macrophage infiltrate) and non-glandular stomach (hyperkeratosis, inflammation and squamous cell hyperplasia) of males and females, in kidney (chronic-progressive nephropathy) of females, and cornea (inflammation) of males.

Neoplasms considered treatment-related were observed in liver, pancreas, testis and in non-glandular stomach. These were all observed in males and no neoplastic lesions were observed in female rats.

Hepatocellular adenoma/carcinoma was observed in 3/65 (4.6%), 3/64 (4.6%), 4/65 (6.2%) and 9/65 (14%) males at 0, 3, 10 and 30 mg/kg/day, respectively. The increased incidence of benign and malignant hepatocellular tumours in males at 30 mg/kg/day was considered test article related.

Acinar cell adenomas of the pancreas were seen in 4/65 (6.2%), 3/64 (4.7%), 6/65 (9.2%), and 10/65 (15%) males at 0, 3, 10, or 30 mg/kg/day, respectively, and acinar cell carcinomas were seen in 1/65, 1/64, 1/65, and 1/65 males in the same respective dose groups. A combined incidence of benign and malignant tumours of pancreatic acinar cells of 5/65 (7.7%), 4/64 (6.3%), 7/65 (11%), and 11/65 (17%). The increased combined incidence of benign and malignant tumours of the pancreatic acinar cells was considered test article-related in males given 30 mg/kg/day.

Benign interstitial cell tumours of the testis were seen in 2/65 (3.1%), 1/64 (1.6%), 4/65 (6.2%), and 12/65 (18%) males given 0, 3, 10, or 30 mg/kg/day, respectively, and were considered test article-related at 30 mg/kg/day.

Squamous cell carcinoma in the non-glandular stomach was observed in 0/65, 1/65 (1.5%), 1/64 (1.6%) and 4/65 (6.2%) males at 0, 3, 10 and 30 mg/kg/day, respectively, and was considered test article related. Squamous cell carcinoma was the cause of death or early sacrifice of all four males given 30 mg/kg/day in which the neoplasm was observed and was considered test article-related in that dose group. Squamous cell carcinoma of the non-glandular stomach is an uncommon tumour in rats on carcinogenicity studies, and the single occurrence of this tumour in each of the 3- and 10-mg/kg/day male groups is of uncertain relationship to the test article. Squamous cell carcinoma of the non-glandular stomach was not noted in any female dose group.

The NOEL for carcinogenicity in the rat study was 3 mg/kg/day in males (AUC_{0-24} 4530 ng*h/mL) and 30 mg/kg/day in females (AUC_{0-24} 23800 ng*h/mL) corresponding to AUC exposure margins of 4/21-fold (M/F) the clinical AUC.

2.5.4.5. Reproductive and developmental toxicity

The reproductive toxicity was performed in rat and rabbit and consisted of studies regarding fertility and early foetal development, EFD, PPND and a juvenile toxicity study. The pivotal studies were preceded by dose range finding studies.

Fertility

No test article effects were observed on reproductive parameters in either sex at any dose level. In males, an increased weight of testis, epididymis, and seminal vesicle relative to total body weight were observed and was considered to be due to the reduction in body weights since no effect was observed on the absolute weights of the reproductive organs. NOAEL for reproduction was 100 mg/kg/day for both sexes. At 100 mg/kg, indications of toxicity were observed with reduced body weights and enlarged liver weights and/or rough liver surface in males. NOAEL for toxicity was 15 mg/kg/day for males and 100 mg/kg/day in females.

Embryofoetal development

In the pivotal EFD study in rat, no maternal effects were observed other than reduced body weight gain and food consumption at the highest dose level of 100 mg/kg/day. No adverse treatment-related effects were recorded regarding anomalies including malformations and variations in the F1 litters at any dose level. The adjusted mean foetal body weight was significantly higher in seladelpar exposed pups compared to controls, however, not dose dependently and considered non-adverse since the weights were increased rather than decreased. NOAEL for maternal toxicity and for F1 litters was 30 and 100 mg/kg/day respectively, with a C_{max} of 6780 and 16900 ng/mL and AUC of 32700 and 159000 ng*h/mL for the respective dose level. The exposure at 100 mg/kg/day was approximately 93-fold higher than the PPARδ EC_{50} value of 182 ng/mL in rat. When comparing exposure at NOAEL of the EFD study to a clinical exposure at 10 mg seladelpar/day, the corresponding AUC-based exposure margin for maternal toxicity and foetal development was x30 and x145 respectively.

In the pivotal EFD study in rabbit, the C_{max} and AUC_{0-24} values increased linearly with seladelpar dose, and metabolites M1, M2 and M3 were detected in the circulation. At the highest dose level of 40 mg/kg/day, the C_{max} was 6770 ng/mL and AUC 44500 ng*h/mL. Maternal effects included reduced body weight and food consumption at the initial phase of dosing period, and reduced body weight gain as recorded on the day of sacrifice. At 2 and 10 mg/kg/day, transient effects of low magnitude in body weight gain and food intake were observed but were considered to be non-adverse. Reduced gravid uterine weight (-17.8%) was observed at necropsy at 40 mg/kg/day. Observations included macroscopic evaluation, live litters, and caesarean section parameters for evaluation of maternal toxicity. The adjusted mean fetal body weight was significantly lower in seladelpar exposed female pups from 10 mg/kg/day and for males from 40 mg/kg/day in comparison to controls. The slight effect on body weights at 2 and 10 mg/kg were considered treatment related but not adverse due to the low level of magnitude. No adverse treatment-related effects were recorded in the F1 litters regarding anomalies including malformations and variations at any dose level. NOAEL for maternal toxicity and F1 litters were 10 mg/kg/day, with a C_{max} of 572 ng/mL and AUC of 2620 ng*h/mL. According to study ID:2300446, seladelpar binds and activates PPARδ in human with almost x5000 higher potency to human ligand binding domain compared to rabbit. Thus, the EFD study in rabbit does not appear to be relevant in the on-target assessment of EFD in humans, however, as the plasma exposure in rabbit was 41-fold above the clinical AUC at a therapeutic dose of 10 mg/day in human, the rabbit adds value as a non-rodent species for evaluation of the potential off-target/secondary pharmacological effects of seladelpar.

No treatment-related foetal external, visceral, or skeletal anomalies were recorded in the EFD studies at exposure levels that were 41-fold and 145-fold above the clinical AUC at 10 mg/day in rabbit and rat, respectively.

Peri-Post Natal Development

Pre- and postnatal development together with maternal function was investigated in rats. Doses up to 100 mg/kg/day were administered to mated females (F0) from gestation date (GD) 6 to lactation date (LD) 20. A slight reduction in body weight gain was observed at 100 mg/kg/day in the F0 generation but was considered non-adverse.

For the F1 generation, no deviations were observed regarding caesarean section data at any dose level. Decreased mean body weight gain from LD 14, LD 7, and LD 0 in the respective groups at 5, 20 and 100 mg/kg/day followed by recovery during the maturation phase at 5 and 20 mg/kg/day. At the highest dose level however, a reduced pup survival was observed between lactational day 4 and 21. All pups in seladelpar-treated groups showed delayed eye opening and pinna unfolding. In the high dose group pups, the balanopreputial cleavage and vaginal opening as well as hair growth were delayed. Reduced body weight gain and food intake was also observed during the maturation phase and at the

following gestational period at 100 mg/kg/day. Transient increase in locomotor activity was observed for F1 males at 100 mg/kg/day. NOAEL, F0: 100 mg/kg/day, and F1: 20 mg/kg/day.

Juvenile toxicity

A dose range finding study on juvenile toxicity from PND 21 to PND 35 was conducted by the applicant in rat. Treatment related findings were lower reticulocyte counts in males and increased albumin/decreased globulin levels in females from 5 mg/kg/day. The latter was also observed in males from 50 mg/kg/day as well as higher platelet counts. Females had higher total protein in plasma at 50 mg/kg/day. Lower body weight gain at the highest dose level (50 mg/kg) -14% and -10% in males and females respectively with reduced food intake in males only.

Seladelpar increased with increased dose level and similarly between sexes. The metabolite levels of M1 and M3 in plasma was 19.5 and 16.4% respectively of seladelpar, while M2 concentrations were higher than seladelpar at all dose levels. Considering that the dose levels were 50% lower than the dose in the EFD study on adult rat, the exposure appears to be similar when juveniles are compared to adult rats except for the highest dose level in adult rats (100 mg/kg/day) where the exposure increased more than dose proportionally.

2.5.4.6. Toxicokinetic data

The toxicokinetics following repeated dosing of oral seladelpar was investigated in mice, rats, dogs and monkeys. Several deficiencies were identified with regards to bioanalysis. Despite these deficiencies, it is concluded that bioanalysis/TK data from the most critical studies can be considered reliable. This includes data for seladelpar in the following studies; 13-week mouse, 26-week rat, 4-, 13- and 52-week monkey, carcinogenicity, EFD rat and EFD rabbit. For the metabolites M1, M2 and M3, reliable data are available from the following studies; 26-week rat, 52-week monkey, EFD rat and EFD rabbit. Additionally, for metabolite M2, reliable data are available from the carcinogenicity studies.

Following repeated oral administration, absorption was rapid with mean time to maximal concentration values generally within the first few hours. The terminal phase t½ varied between species, ranging from 1 to 11 hours in mice, 2 to 15 hours in rats, 5 to 47 hours in dogs and 4 to 43 hours in monkeys. Systemic AUC exposure to seladelpar increased in a dose-dependent manner; however, exposures significantly decreased after repeated daily dosing in rats and monkeys, suggestive of possible autoinduction leading to increased metabolism of seladelpar over time. There are no consistent sex differences in exposure of seladelpar. However male rats seem more sensitive to seladelpar toxicity.

The AUC margins at NOAEL in the repeat-dose studies were around 5/13 (M/F) in the 26-week rat study and 2/11 (M/F) in the 52-week monkey study. Substantially higher margins of around 100 were evident in the rat fertility study, and in the rat and rabbit embryofoetal developmental studies. In the pre- and post-natal development study, the margin was around 15.

2.5.4.7. Local Tolerance

The local tolerance of seladelpar in the gastrointestinal tract was evaluated in the repeat-dose toxicity studies. In rats, epithelial hyperkeratosis of the non-glandular stomach and oesophagus was observed following 14 days to 26 weeks repeated oral administration. This is considered a rodent-specific response to irritation following the oral gavage. Seladelpar is classified as a mild eye irritant when evaluated in an *in vitro* bovine corneal eye irritation test.

2.5.4.8. Other toxicity studies

Immunotoxicity

Seladelpar did not show potential for immunotoxicity in the repeat-dose toxicity studies and no sensitisation potential was recorded in the local lymph node assay in mouse.

Metabolites

Following 14 days daily dosing in patients (10 mg/day), it is noted that the AUC exposure of metabolites M1, M2 and M3 are about 0.4-fold, 3-fold and 0.6-fold the seladelpar AUC exposure. According to ICH M3 Q&A, metabolites M1 and M3 can be considered qualified if the exposures in animals reach 50% of the human exposure. Thus, M1 and M3 are considered qualified in the repeat-dose, embryo-foetal development, and *in vivo* genotoxicity studies. In the carcinogenicity studies, although the exposure of metabolites M1 and M3 were analysed by a non-validated assay, it seems reasonable to assume that they were present at exposures above the clinical exposure, and also qualified in these studies.

For M2, being a major metabolite that exceeds seladelpar exposure by about 3-fold in humans, it is appropriate for exposure to the metabolite in animals to exceed that in humans (ICH M3 Q&A). This is the case throughout the non-clinical study package. Overall, the human major metabolites M1, M2 and M3 are considered qualified throughout the non-clinical study package.

Impurities

In the drug substance, solfoxides M1a and 1b (diastereomeric isomers), and des-ethyl M2 are specified at ≤0.30%, 0.30% and 0.50%, respectively. The qualification threshold is 0.15% according to ICH Q3A(R2). In the drug product, the qualification threshold is 0.5% according to ICH Q3B(R2). The proposed specification of solfoxide M1-a, and M1-b at release is ≤2.0%, respectively. Sulfoxide M1-a and sulfoxide M1-b are major metabolites in humans and these metabolites are observed in plasma in all toxicology species. These metabolites are considered qualified throughout the non-clinical study package, and the proposed specifications are acceptable.

Phototoxicity

Seladelpar was negative for phototoxicity in BALB/c 3T3 fibroblast cells *in vitro*. Given that seladelpar show no light absorption within the range of natural sunlight (290-700 nm), no study would have been warranted (ICH S10).

Mechanistic studies

The applicant has performed mechanistic studies to further investigate the mode of action of seladelpar. The *in vitro* study from mouse, monkey and human hepatocytes did not show any induction of mitogenic activity by seladelpar or M2 in any of the studied species. The co-culture of hepatocytes from mouse, rat, monkey and human and Kupffer cells from rat and human suggested no mitogenic activity for mouse, rat or monkey cells; inconsistency of the data was observed in human cells suggesting weak or no stimulation of DNA synthesis in human cells.

The mechanism for liver carcinogenesis observed in rodents was investigated in several *in vivo* studies to clarify if the MoA is PPARα dependent (rodent-specific MoA), and if sufficient activation of PPARδ (human specific MoA) was achieved in rodent carcinogenicity studies to be able to conclude of the PPARδ activation has been sufficiently investigated during the non-clinical programme.

Peroxisome proliferation was evaluated in the livers of mice (13-week study) and rats (101-week study), suggesting peroxisome proliferation correlating with increased liver weights and hepatocellular hypertrophy observed in male and female mice and dose-related increases in PMP70 labelling in all treatment groups of rats, suggested to correlate with peroxisome proliferation. The 14-day study in the PPARα null mice showed that wild-type mice are more sensitive to liver effects that PPARα null mice, suggesting that PPARα plays a role in the observed liver effects in mice. The livers from monkeys (3-month study) were also quantified for peroxisome proliferation, suggesting minimal peroxisome proliferation correlating with recorded increase of liver weights and hepatocellular hypertrophy in seladelpar-treated monkeys.

These supportive studies further strengthened the MoA hypothesis and the species difference in the sensitivity for peroxisome proliferation, corresponding with liver effects recorded in seladelpar-exposed animals.

2.5.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, default/refined	0.0020	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

Substance: Seladelpar Lysin Dihydrate			
CAS-number: 851528-79-5 (seladelpar) 928821-40-3 (seladelpar lysine dihydrate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107/117/123	4.73	Potential PBT: Y
Partition coefficient (Log D_{ow}, at pH 7.4)		1.95	N
Pka		3.20	

The Log Dow value has only been determined at pH 7.4. Since the Log Dow values should be performed within the full environmentally relevant pH-range (at least 3 pH values ranging from pH 5 to 9), the applicant has committed to investigate the Log Dow values within the full pH-range using the Shake Flask method (OECD 107, OPPTS 830.7550/830.7570). The report will be available from end of April 2025. If the Dow value at any pH value between pH 5 and pH 9 meets the trigger values for assessment of secondary poisoning (log Kow ≥ 3) or PBT/vPvB assessment (log Kow > 4.5), further assessments will be conducted.

2.5.6. Discussion on non-clinical aspects

Pharmacology

A number of *in vitro* and *in vivo* studies have been conducted to demonstrate mechanism of action and pharmacodynamic activity of seladelpar.

Seladelpar activity was addressed in cell-based reporter gene assays (GAL4) using human, rat, mouse, hamster, rabbit and monkey ligand binding domains of PPAR-α, δ, γ. Seladelpar activated human PPARδ with the highest selectivity and potency among the tested species. The seladelpar EC_{50} values for activation of PPARδ in different species were the following: human 0.002 µM; Cynomolgus monkey

0.017 µM; rabbit 9.6 µM; rat 0.41 µM; mouse 0.12 µM. No substantial activity was observed on PPARδ in rabbit.

In mice, seladelpar was shown to activate PPARδ responsive gene expression in the livers in an *in vivo* study in both wild type and PPARα-K/O mice at exposures comparable with the 2-year carcinogenicity study in mice. In addition, seladelpar induced PPARα responsive gene expression in wild type mice only, at 3 and 20 mg/kg/day.

M2 is pharmacologically active in human, and all investigated non-clinical species, while the metabolites M1 and M3 had no relevant activity against human PPARs.

No off-target activity was shown of seladelpar in a panel of 48 receptors, transporters, and ion channels. In addition, seladelpar and the active metabolite M2 had no activity in a battery of 15 nuclear- and 1 non-nuclear human receptors. None of the metabolites were completely evaluated in the secondary pharmacology studies, however, according to the plasma concentrations in non-clinical species, the metabolites appear to be covered.

Safety pharmacology aspects of seladelpar were evaluated in a number of studies, *in vitro* and *in vivo*. The pivotal non-clinical studies were conducted in accordance with regulatory guidelines. No treatment-related effects on cardiovascular, respiratory or CNS safety were observed in any test system. However, the metabolites (M1, M2, M3) were not studied for hERG inhibition, but since no signs of QT-prolongation was observed in clinical trials, the likelihood of metabolite-mediated hERG inhibition appears unlikely.

Pharmacokinetics

The applicant has provided during the procedure sufficient information regarding analytical methods, validations, and bioanalysis, in relation to each study.

Re-validation of a bioanalytical methods after analysis of samples (and in another facility) cannot be considered regulatory acceptable. The bioanalytical data from the following studies can therefore not be viewed as fully validated for seladelpar or metabolites: TOX6340, TOX6341, TOX6342, TOX7088 and TOX7387.

The status for validations of bioanalytical method used for quantitation of seladelpar and metabolites is summarised for GLP toxicity and safety studies in the table below. The general assessment is that there is TK data that is acceptable to evaluate the results.

Specificity appeared to be mixed-up with selectivity in the validations. Interference caused by metabolites of the drug was requested to be investigated. The applicant discussed the issue, emphasizing that the molecular weights of metabolites are different from that of seladelpar, and a baseline chromatographic separation of metabolites and seladelpar is assured in methods. Also, calibration data in standard curves of seladelpar and its metabolites (including the LLOQ) were back calculated and both % CV and %DEV met the applicable at the time guideline requirement. The probability that seladelpar and its metabolites mutually interfere with each other's bioanalytical results is considered very low.

Pharmacokinetic and toxicokinetic studies with seladelpar have been conducted in mice, rats, rabbits, dogs, and monkeys. A total of 6 studies in mice, 10 studies in rats, 2 studies in rabbits, 3 studies in dogs and 5 studies in monkeys have been submitted presenting plasma exposure data.

In general, after oral administration, seladelpar is readily absorbed with high bioavailability. Overall, in all species, the systemic exposure of seladelpar (AUC) increased in a dose-dependent manner. Accumulation appeared to be species specific. In rats and monkeys, seladelpar AUC significantly

decreased by repeated daily dosing possibly explained in rats by induction of CYP3A isoforms. There are no consistent sex differences in exposure of seladelpar.

Seladelpar and M2 are highly bound to plasma proteins, primarily HSA, in all species tested, including humans. Although the concentrations tested (200 – 20 000 ng/mL) are quite high, the lowest is in the range of human exposure and higher concentrations cover exposure in toxicology studies, which is considered adequate. The free fractions for seladelpar are in the range of approximately 0.2-0.5% and for metabolite M2 the range is 0.6-1.1% with small species differences, i.e. not expected to affect the exposure marginals for the toxicity studies.

Seladelpar was widely distributed in rats, as demonstrated by quantitative whole-body autoradiography (QWBA) data in both non-pigmented and pigmented rats with the highest radioactivity detected in the liver, kidney, and bladder. No indication of melanin binding of radioactive material was found, and data indicate complete elimination following an oral dose of ^{14}C-seladelpar.

No tissue distribution data is submitted for any other species. Neither are any data regarding distribution in blood cells, across the Blood Brain Barrier, over the placental or excretion in milk. The SmPC informs that it is not known whether seladelpar or its metabolites are excreted in human milk which is acceptable.

Seladelpar is mainly metabolised by CYP enzymes across all species, including humans. In rats, dogs, monkeys, and humans the *in vitro* metabolic profile was qualitatively similar. Three main metabolites were found circulating in plasma, sulfoxide (M1), o-desethyl (M2) and o-desethyl sulfoxide (M3), with M2 metabolite being the most predominant in most species.

No human-specific metabolites are observed in the *in vitro* studies. Species comparisons of identified metabolites indicated that none of the identified metabolites is human-specific.

In the metabolite profiling that was done in connection with human Study CB8025 11734, there are plasma radio-chromatograms with unidentified peaks. However, as these peaks are very small, it is considered acceptable that they are not identified.

Study FK5497, which compares *in vivo* metabolite profiles in human and monkey plasma (from study 800025-NAP-1001 and TOX6919 respectively), does not show any human-specific metabolites. The pooled human plasma only covers the time span 0-3h, possibly not covering metabolites appearing later. However, the urinary (unhydrolysed and hydrolysed) data for 0-96 hours are considered sufficient to cover late appearing metabolites since urinary excretion of seladelpar-related material is the major route of elimination in humans. The CHMP noted that study NAP-1001 was an early clinical study conducted in 2005, and the metabolites identified in human plasma in this study are only a few of those identified in study CB8025-11734.

In rat, which is the only studied animal species regarding excretion, the predominant route of elimination for seladelpar is via feces, mainly as metabolites secreted into the bile. Urinary elimination appeared to be a minor pathway. In contrast, urinary excretion of seladelpar-related material, mainly metabolites, is the major route of elimination in humans.

Toxicology

The toxicity of seladelpar has been investigated in the comprehensive battery of *in vitro* and *in vivo* studies in agreement with applicable guidelines. The selection of multiple species for the non-clinical programme was justified by the sensitivity differences towards PPARs between species. However, it can be questioned if all studies with selected species were relevant and if the non-clinical programme was carefully planned with respect to 3R principles.

To obtain further mode of action information on potential toxicities, additional parameters were added to certain pivotal toxicity studies, including electron microscopy of liver, heart, skeletal muscle and/or kidney (13-week rat, 26-week rat, 4-week monkey, 52-week monkey); biochemical markers of PPARα activation (26-week rat, 4-week monkey, 52-week monkey); PMP70 (also denoted Abcd3, a marker of peroxisome proliferation) immunohistochemistry and morphometric analysis of liver (13-week mouse, 13-week monkey); heart histomorphometric assessments and Oil red-O staining for lipid (26-week rat, 52-week monkey); and oesophagus cell Ki-67 proliferation assessments (52-week monkey).

As further discussed in the pharmacology section, due to species differences in PPARδ potency and selectivity versus PPARα, the biological activity of seladelpar varies between species. In this aspect, the monkey is the species with closest similarities to humans. As PPARδ and α are widely expressed and may have overlapping functions, the interpretation on study findings and the clinical relevance are not straightforward.

In repeat-dose toxicity studies, the dose-limiting toxicity in most species include marked body weight loss associated with pronounced effects on food consumption. These adverse effects caused termination of several animals. These effects are considered likely related to both PPARα and PPARδ agonism.

Adverse effects seen in most species include effects in liver, in skeletal muscle and on RBC-related parameters. Findings in liver include dose-related increases in liver weight accompanied by hepatocellular hypertrophy, necrosis and elevations of ALT and AST. The findings were reversible and more severe in rats than in monkeys. Electron microscope evaluation demonstrated peroxisome proliferation in liver and induction of CYP4A and FCoA in the rat 26-week study at ≥5 mg/kg/day. In monkeys, peroxisome proliferation was also apparent by electron microscope evaluation in liver, and hepatic CYP4A and FCoA were induced at as low as 1 mg/kg/day. Collectively, these data suggest that PPARα agonism may be involved in the liver toxicity. The applicant argues that based on a 630-fold lower affinity of seladelpar for human PPARα (EC_{50} 1.26 µM ~ 0.56 ng/mL) compared to PPARδ (EC_{50} 0.002 µM ~ 0.0009 ng/mL) in cell-based reporter gene assays, liver toxicity is less likely in patients. However, hepatotoxicity in the form of ALT elevations occurred in PBC patients in a clinical study with higher doses of seladelpar (50 mg and 200 mg, see section 3.3.7). SmPC section 4.4 contains warnings for dose-related increases in serum transaminases (AST and ALT), and routine monitoring of transaminase levels is recommended.

Dose-related reductions in red blood cell mass (red blood cells, haemoglobin and haematocrit) with corresponding decreases in reticulocyte counts were observed in rats, mice, monkeys and dogs, primarily at high seladelpar exposures. The NOAELs for haematology effects provided AUC margins of >200-fold in the 13-week mouse study, >10-fold in the rat 26-week study, and >20-fold in the 52-week monkey study. The applicant proposes that the effects on the red blood cell compartment may be a general high dose toxicity effect, this is agreed by the CHMP.

Dose-related increases in kidney weight was observed in mice, rats and monkeys, but not in dogs. With a few exceptions, there were no microscopic correlates or findings in urinalysis. In the 26-week rat and the 52-week monkey studies, electron microscope evaluation demonstrated peroxisome proliferation in kidney and induction of CYP4A and FCoA, indicating PPARα activation. It is possible that the increased peroxisome proliferation may have contributed to the increased kidney weights.

Minimal to moderate, reversible skeletal muscle degeneration was observed at high doses in female rats in the 13-week study, in monkeys and mice treated for 13 weeks, and in dogs 4 weeks seladelpar administration. There was no skeletal muscle degeneration observed in the rat 26-week or in the monkey 52-week studies when tested up to AUC exposures of at least 70 and 24-fold, respectively, above the clinical therapeutic AUC exposure. The applicant is of the opinion that the finding is related

to PPARα activation. In rodents, activation of PPARα is known to induce skeletal muscle degeneration and necrosis resulting from increased mitochondrial and peroxisomal β-oxidation of fatty acids leading to oxidative stress and tissue damage (Faiola 2008). In available clinical data, the reported muscle-related TEAEs revealed no safety concerns. Altogether, based on the large exposure margins, a likely PPARα mechanism and the available clinical data, the skeletal muscle degeneration observed in all species at high exposures is not considered a clinical concern.

Published data are available indicating involvement of PPARδ in the differentiation of chondrocytes. Therefore, the applicant was asked to discuss the potential risk for effects on chondrocytes following seladelpar treatment. Available data indicate no cartilage or bone abnormalities in the performed repeat-dose studies in mice, rats, dogs, or monkeys. Furthermore, no adverse effects on long bone development were observed in a preliminary juvenile toxicity study where rats were dosed with seladelpar from post-natal Day 21 to post-natal Day 35. Thus, the available non-clinical data have not identified a risk related to chondrocytes.

Findings in adrenal gland were observed in rats and monkeys. The adrenal gland findings were fully reversible in the 13-week rat study and showed a partial resolution in the rat 26-week and in the monkey 13-week studies. It is noted that adrenal gland was an organ with "medium" [^{14}C]-seladelpar-derived radioactivity, but it was only detected at the 2-hour time-point. Although the finding is of unknown aetiology, the morphologic changes are consistent with that of an adaptive stress response commonly seen in laboratory animals, and the findings are considered of limited clinical relevance.

Some findings were only seen in a single species. These include minimal to mild reversible cytoplasmic vacuolisation of the urinary bladder epithelium in some monkeys in the 52-week study. It should be noted that there is no information on the excretion route in monkeys. In rats, the majority of total radioactivity is excreted via feces while urinary excretion is the major route of elimination for total radioactivity in humans.

Effects in male reproductive organs were only observed in dogs at high doses and include minimal to moderate degeneration of the seminiferous tubules of the testis, interstitial cell atrophy and atrophy of the prostate gland. The testicular seminiferous tubule degeneration and prostatic atrophy may have been related to the testicular interstitial cell atrophy since the interstitial cells secrete testosterone, which is needed for spermatogenesis and prostate stimulation. There were no effects observed in the male reproductive organs in chronic rat and monkey studies, as well as no effects on fertility in male rats at up to 100 mg/kg/day (223-fold the human clinical AUC). While direct toxic effects cannot be ruled out, it is speculated that the emaciated condition of the dogs may have affected the male reproductive system with reference to Rehm (2008). This article describes that reduced food consumption and associated lower body weights have a negative impact on the male reproductive system in rats. If this is applicable also to dogs is not known, although lower body weights and a corresponding decrease in food consumption were observed at doses causing the effects. Given the observation in one species only, and at high exposures, the finding is likely not of clinical relevance. The reversibility of the testicular changes could not be evaluated due to the early euthanasia of the high dose male recovery animals.

In rats only, effects in the GI tract (oesophagus and non-glandular stomach), cardiac muscle and thyroid were observed. Epithelial hyperkeratosis of the non-glandular stomach and oesophagus was observed following 14 days to 26 weeks repeated administration. Although the minimal hyperkeratosis in the oesophagus could have significance beyond rodents, similar findings were not observed in dogs or at dosing durations up to 52 weeks in monkeys and at higher systemic exposures. In the 52-week monkey study, a lack of proliferation was confirmed in the oesophagus epithelium by Ki67 immunohistochemistry. Therefore, epithelial hyperkeratosis of the non-glandular stomach and oesophagus is considered rat-specific findings in response to local irritation and not relevant for human

risk. It should be noted that tumours in the non-glandular stomach were observed in the mouse and rat carcinogenicity studies.

Minimal to slight cardiac muscle degeneration and/or necrosis was observed in male rats in the 13-week toxicity study and progressive cardiomyopathy was noted in males in the 26-week rat study. The findings were reversible in the 13-week study but not in the 26-week study. In the 2-year rat 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. No cardiac muscle degeneration was observed in mice dosed for 13 weeks or in monkeys dosed for 52 weeks (AUC up to ~ 277- and 24-fold the clinical AUC in mice and monkeys, respectively). Histomorphometric analysis did not reveal any changes in the size of heart structures in chronic studies in rat through 26 weeks or in monkey through 52 weeks. Although PPARδ (and PPARα) receptors are found in the heart, this finding may be related to an exacerbation of the common progressive cardiomyopathy observed in rats where male rats tend to be more affected. The clinical relevance is likely low.

The finding of minimal thyroid follicular cell hypertrophy in rats is likely a consequence of an increased rate of hepatic thyroxine (T4) glucuronidation and subsequent biliary excretion. An increased rate of T4 excretion results in lower T4 blood levels which triggers an increase in the release of pituitary-derived TSH, resulting in thyroid follicular cell hypertrophy. Although an effect on TSH was not observed, many inducers of hepatic cytochrome P450 isoenzymes in the rat are known to secondarily cause thyroid follicular cell hypertrophy by this mechanism. Due to differences in T4 half-life, thyroglobulin binding, and the ease of UDP-glucuronyl-transferase induction, rats are much more susceptible than humans to secondary thyroid follicular cell hypertrophy. Therefore, no adversity on thyroid is expected in patients.

With regards to genotoxicity, seladelpar was tested in a complete package of GLP genotoxicity studies in agreement with ICH S2(R1) guidance and is concluded as negative for genotoxic potential. Based on the totality of data, it seems reasonable to conclude that metabolites M1, M2 and M3 have been evaluated for genotoxicity *in vitro* and *in vivo* and can be concluded as negative for genotoxic potential.

In the carcinogenicity studies, tumours considered test article-related were observed in liver and non-glandular stomach in both species, and in the testis and pancreas of high-dose male rats only.

The applicant is of the opinion that the squamous cell carcinoma in the non-glandular stomach do not constitute a human risk with reference to Proctor (2007). In the repeat-dose studies, epithelial hyperkeratosis of the non-glandular stomach and oesophagus was observed in rats following 14 days to 26 weeks repeated administration, which is considered likely a rodent-specific finding in response to irritation. The epithelial hyperkeratosis in the oesophagus at doses ≥5 mg/kg/day could have significance beyond rodents, but similar findings were not observed in monkeys in studies up to 52 weeks. Therefore, it is agreed that these tumours do not constitute a human risk.

The applicant is further of the opinion that the combination of liver tumours in mice and liver, pancreas and testis tumours in rats are considered likely resulting from PPARα agonism. Extensive MoA investigations indicated a PPARα-dependent mechanism for the liver carcinogenesis in mice and rats.

While this is partly agreed, given seladelpar's potency and selectivity in rodents, both PPARδ and PPARα may contribute to the observed malignancies in rodents making the interpretation of the carcinogenicity study results difficult. Based on this uncertainty, a MO was raised on carcinogenicity where the applicant was asked to discuss the available recent literature in more depth with regards to the relation between PPARδ agonism and malignancy as recommended in a CHMP advice. Further, to provide support that a potential carcinogenic risk in humans related to PPARδ agonism has been

adequately evaluated in the seladelpar carcinogenicity studies. Information on clinical experience (i. e. malignancy risk) of approved products with documented PPARδ agonistic activity, if available, was also requested.

In the response, the applicant clarified that an in-depth review with regards to the relation between PPARδ agonism and malignancy dated 2018 (post CHMP advice) was submitted at the time of MAA, however in a module 5. The conclusion of this review is that based on the weight of evidence analysis that an association between PPARδ and cancer enhancement is unlikely, with some evidence that on-target metabolic and anti-inflammatory effects due to PPARδ activation could be associated with beneficial anti-cancer effects. However, it should be noted that other opinions are also found in literature, and no consensus position is available.

Further, the applicant is of the opinion that PPARδ has been adequately tested in the mouse and rat carcinogenicity studies as the C_{max} exposures provided multiples above the PPARδ EC_{50}s in the reporter gene assays at all dose levels. Multiples of up to 283- and 71-fold the respective PPARδ EC_{50} were evaluated in mice and rats, respectively. Based on this, the CHMP agreed that a substantial PPARδ activation was obtained in the mouse and rat carcinogenicity studies, and that the studies can be considered relevant for human risk assessment. These data together with a study in which seladelpar was dosed orally once daily for 14 days at 3 and 20 mg/kg, and induced expression of both PPARδ- and PPARα-regulated genes in the livers of mice, indicate that PPARδ receptor was activated at exposure levels relevant to those in the mouse carcinogenicity study. The CHMP also noted that *in vitro* data indicate that seladelpar is a more potent agonist of PPARδ than of PPARα in all species; in mice (~53x), rats (~12x) and in monkeys (>100x). This is agreed by the CHMP.

Rodent carcinogenicity data from compounds with a reported agonistic activity on PPARα, PPARδ and/or PPARγ (bezafibrate, elafibranor and GW501516), all reveal a tumour profile characteristic of PPARα activation. Additional tumours in several tissues, not attributed to PPARα, were reported for GW501516. The potential link between these tumours and PPARδ agonism cannot be evaluated without further information of the characteristics of this compound. Clinical use of bezafibrate, is not reported to be associated with an increased risk of malignancy, although it is unclear how well this has been studied/documented. Hence this issue was not further pursued.

Overall, it is concluded that the potential for any PPARδ-mediated effects of seladelpar have been fully evaluated. The carcinogenicity studies in rats and mice with seladelpar demonstrate that long-term administration of a PPARδ agonist does not produce tumours in either species in tissues (colon, breast, brain, lung and skin) that could be targets of PPARδ-mediated tumorigenesis, given the known PPARδ expression in these tissues. This conclusion is further supported by absence of any genotoxic effects based on *in vitro* and *in vivo* genotoxicity studies and lack of demonstrated effects on immune cells.

The combination of liver tumours in mice and liver, pancreas and testis tumours in rats are likely resulting from PPARα agonism. No clear arguments have been provided supporting that PPARδ agonism is not likely to contribute to the observed tumours. It is however acknowledged that extensive MoA investigations have been performed indicating a PPARα-dependent mechanism for the liver carcinogenesis in mice and rats.

Of uncertain relation to treatment are benign epithelial ovarian neoplasms (adenoma, cystadenoma and tubulostromal adenoma) observed at higher incidences in the low (5 mg/kg/day) and intermediate dose (10 mg/kg/day) groups (11 and 12%, respectively) than that in the control (1.6%) and high dose (4.6%) groups. Of these lesions, the majority were benign adenomas/cystadenomas with one exception of 1 tubulostromal adenoma observed at 10 mg/kg/day (1.6%) The applicant was asked to provide historical control data from the Test Facility, and to discuss the potential relation to treatment and clinical relevance. Historical control data from the Test Facility report a total mean incidence of adenomas/cystadenomas of 2.6% (range 0 to 6.7%), while the total incidence of tubulostromal

adenomas were lower, 0.2% (range 0 to 3.4%). Thus, the incidences of adenomas/cystadenomas at 5 and 10 mg/kg/day are above that reported in the historical control data. The applicant is of the opinion that the slight, but non-dose-related, increase in benign ovarian epithelial neoplasms is of very low risk to patients. This position is agreed. Literature provide support that ovarian epithelial neoplasms may result from remnant mesonephric ductular structures in CD-1 mice. Moreover, given the lack of dose/exposure response, the lack of any evidence of genotoxicity for seladelpar, the lack of seladelpar-related preneoplastic or toxicity changes in the ovary of the mouse, and the lack of any treatment-related ovarian pathology findings for seladelpar in the rat carcinogenicity study, it is considered that the benign ovarian epithelial neoplasms are not likely to constitute a human risk.

In the mouse 2-year study, an increased incidence of lens cataracts was observed in males at the high dose (45% versus 31% in controls), and in all female dose groups (dose-related, 31, 34 and 48% versus 17% in controls). The incidence of cataracts in all study groups, including controls, was high compared to the Historical Control Data (0-10.9% in males; 0-7.3% in females). As noted by the applicant, lens cataracts are common background lesions in aged CD-1 mice, and incidences up to 25% have been reported in literature. Mukaratirwa 2015 studied histopathological findings in eyes of untreated mice at 4, 13, 80, and 104 weeks, and report lens cataract incidences of 0, 0, 0.44% and 12.71% in female CD1 mice, respectively. Similar findings were noted in male mice. Based on these data, it seems clear that the incidences increase by aging.

Given the dose-response relation, the finding is considered likely seladelpar-related and may be a species-specific exacerbation of this spontaneous aging lesion in CD1 mice, as suggested by the applicant. Bezin et al (2019) report that prolonged use of fibrates (e.g. PPARα agonists) is associated with an increased risk for cataract surgery. The proposed mechanism for this observation is that the eye lens membrane cells require high cholesterol concentrations that might be counteracted by lipid-lowering drugs. Seladelpar is not expected to cause significant PPARα activation in patients, but some decreases in serum cholesterol were observed. In clinical data to date, there are no clear imbalance in cataracts between treated and placebo groups, although long-term data are not available.

No apparent relationship between serum cholesterol and lens cataracts was observed in the non-clinical data. Clinical chemistry evaluations were not included in the mouse carcinogenicity study, but in the 13-week mouse study, there was no seladelpar-related change in cholesterol reported in males at any dose, and mean cholesterol was increased up to 1.59-fold over control mean in females at ≥25 mg/kg/day. Lens cataracts were not observed in the 26-week and 2-year rat carcinogenicity studies or in the 52-week cynomolgus monkey study. Overall, it is agreed that the clinical risk following long-term seladelpar treatment seems low.

The reproductive toxicity was performed in rat and rabbit and consisted of studies regarding fertility and early foetal development, EFD, PPND and a juvenile toxicity study. The pivotal studies were conducted according to current regulatory guidelines under GLP regulations and were preceded by dose range finding studies. Seladelpar binds and activates PPARδ in human with almost x5000 higher potency to human ligand binding domain compared to rabbit and x200 compared to rat. However, in the EFD study on rat the NOAEL value was 30 mg/kg/day for maternal toxicity and 100 mg/kg/day for embryo-foetal development. The maximum plasma exposure (C_{max}) at the highest dose level was 16900 ng/mL i.e., 93-fold higher than the rat PPARδ EC_{50} of 182 ng/mL. The AUC-based safety margin over clinical exposure (at 10 mg/day seladelpar) for developmental toxicity was >145. In addition, pharmacological response could be observed in rats already at a dose level of 3 mg/kg/day for two weeks in the PPARδ responsive gene expression assay performed on liver. While the rabbit adds value as a non-rodent specie for evaluation of the potential off-target/secondary pharmacological effects with a 41-fold AUC-based safety margin over clinical exposure (at 10 mg/day seladelpar), the rat is considered to have sufficient systemic exposure for evaluation of PPARδ related effects on embryofetal toxicity.

Regarding the environmental risk assessment, the Log Dow values should be performed within the full environmentally relevant pH-range (at least 3 pH values ranging from pH 5 to 9) but has only been determined by the applicant at pH 7.4.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of seladelpar to the environment.

The applicant commits to perform the following studies as follow-up measures:

To investigate the Log Dow values within the full pH-range using the Shake Flask method (OECD 107, OPPTS 830.7550/830.7570). The report will be submitted end of April 2025.

If the Dow value at any pH value between pH 5 and pH 9 meets the trigger values for assessment of secondary poisoning (log Kow ≥ 3) or PBT/vPvB assessment (log Kow > 4.5), further assessments will be conducted.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view the product is approvable. The major objection regarding the carcinogenicity evaluation and malignancy risk that was raised at Day 120 is considered resolved, and it is agreed that PPARδ agonism has been adequately evaluated in the mouse and rat studies, and that the tumours observed in liver, testis, pancreas and non-glandular stomach are not considered to be of human relevance.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

To investigate the Log Dow values within the full pH-range using the Shake Flask method (OECD 107, OPPTS 830.7550/830.7570). The report will be submitted end of April 2025.

If the Dow value at any pH value between pH 5 and pH 9 meets the trigger values for assessment of secondary poisoning (log Kow ≥ 3) or PBT/vPvB assessment (log Kow > 4.5), further assessments will be conducted.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioavailability Study Reports								
NAP-1005	5.3.1.1	Evaluate the bioavailability of seladelpar hard gelatin capsule relative to a solution formulation	Open-label, 2-way crossover study in healthy male subjects	Oral/ hard gelatin capsule= 100 mg Solution/ formulation= 100 mg/ml	12 planned 13 analyzed	Healthy male subjects	1 day, single dose	Complete [29Aug2005-07Oct05]
CB8025-11836	5.3.1.1	Evaluate the relative bioavailability of seladelpar 10 mg capsule and tablet formulations following oral administration in healthy subjects	Open-label, crossover study in healthy subjects	Oral/ hard gelatin capsule=10 mg neat drug substance Hard gelatin capsule=10 mg Formulation 2 Tablets=10 mg	16 planned 16 analyzed	Healthy male and female subjects	7 weeks	Complete [04Apr2018-08May2018]

Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of Hepatic Metabolism and Drug Interaction Studies								
CB8025-11732	5.3.2.2	Evaluate the PK of seladepar and its metabolites in M1, M2, and M3 in subjects with varying degrees of hepatic impairment compared to healthy matched control subjects with normal hepatic function	Phase 1, open-label, non-randomized study	Oral/ hard gelatin capsule=10 mg	32 planned 32 analyzed	Healthy male and female subjects	Single dose	Complete [15Nov2017-15May2018]
CB8025-21838	5.3.2.2	Evaluate the effect of hepatic impairment on the PK of seladelpar following oral dosing of seladelpar to subjects with PBC and hepatic impairment	An open-label study	Part A: Oral 10 mg Part B: Multiple, oral, 10 mg doses	Part A: 18 (Cohorts 1, 2, and 3 complete) Part B: 17 (Cohorts 1 and 2 complete, 5 out 6 patients completed for Cohort 3)	PBC with varying degrees of HI	Part A: 1 day Part B: 28 days	Ongoing

Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetics Studies								
NAP-1001	Module 5.3.3.1	Comparative BA study under fasted and fed conditions. Part 1: Safety, tolerability, PK, PD of RWJ-800025 and its metabolites M1 and M2	Two-part, randomized, double-blind, placebo-controlled study in healthy male subjects	Part 1: Oral 1, 5, 15, 60, 120, 360 mg	Part 1: 18 planned 20 analyzed	Healthy male subjects	Single dose	Complete [17Nov2004-04Apr2005]
		Part 2: Effect of food on safety, tolerability, PK, and PD of RWJ-800025 and its metabolites M1 and M2		Part 2: 120 mg oral dose (powder for oral solution) fasted or fed	Part 2: 8 planned 7 analyzed	Healthy male subjects		
CB8025-11734	5.3.3.1	Define the PK and disposition and characterize the mass balance of radioactivity of seladelpar and its metabolites following a single oral dose of [^{14}C] seladelpar	Open-label study of the absorption, metabolism, and excretion of [^{14}C] seladelpar	Oral/ hard gelatin capsule=10 mg	8 planned 8 analyzed	Healthy male and female subjects	Single dose	Complete [17Oct2018-29Nov2018]

CB8025-11840	5.3.3.1	To evaluate: The effect of a single oral dose of fluconazole, a cytochrome P450 (CYP) 2C9 inhibitor, on the PK of seladelpar The effect of repeated oral doses of carbamazepine, a CYP3A4 inducer, on the PK of seladelpar The effect of repeated oral doses of probenecid, an organic ion transporter 3 (OAT3) inhibitor, on the PK of seladelpar The effect of a single oral dose of quinidine, a P-glycoprotein (P-gp) inhibitor, on the PK of seladelpar The effect of a single oral dose of cyclosporine, an inhibitor of breast cancer resistance protein (BCRP) and OATP1B1 and OATP1B3, on the PK of seladelpar The effect of a single oral dose of seladelpar on the PK of rosuvastatin, a BCRP substrate	Open-label, 6-arm, fixed-sequence	Oral/ hard gelatin capsule=10 mg	96 planned 93 analyzed	Healthy male and female subjects	Single dose	Complete [22June2021-30Oct2021]
CB8025-11942	5.3.3.3	To assess the PK of a single dose of seladelpar in subjects with renal impairment compared to healthy subjects with normal renal function To evaluate the safety and tolerability of a single dose of seladelpar in subjects with renal impairment, and in healthy subjects with normal renal function	Open-label pharmacokinetic study	Oral/ hard gelatin capsule=10 mg	48 planned 36 analyzed	Male and females with mild, moderate, or severe renal impairment	Single dose	Complete [16Jun2021-09Dec2021]

Reports of Human Pharmacodynamics Studies								
NAP-1002	5.3.4.1	Part 1: Safety, tolerability, PK, PD	Randomized, placebo-controlled	Oral/ Part 1: 50, 100, 200 mg	Part 1: 36 planned 36 analyzed	Part 1: healthy male subjects with low to normal HDL-C	Single dose Days 1 to 21	Complete [22Jun2005-27Oct2005]
		Part 2: Safety, tolerability, PK, and CYP3A4 enzyme induction potential of seladelpar		Part 2: [single dose Days 3 to 16] (Midazolam=as 20 mg/2 ml solution)	Part 2: 12 planned 12 analyzed	Part 2: healthy male subjects using midazolam	Single dose Days 3 to 16	
NAP-1003	5.3.4.1	Evaluate the PK effects of a single oral dose of seladelpar on a single oral dose of simvastatin	Exploratory open-label, single dose, randomized, 2-way crossover	Oral / 200 mg [single dose] (Simvastatin dose=80 mg)	12 planned 12 analyzed	Healthy male subjects	Single dose	Complete [12Sep2005-15Oct2005]
NAP-1004	5.3.4.1	Evaluate the PK effects of singe oral dose of seladelpar on concomitant administration of tolbutamide	Exploratory open-label, randomized, 3-way crossover	Oral / 200 mg [single doses] (Tolbutamide= 500 mg tablet)	15 planned 15 analyzed	Healthy men genetically identified as extensive metabolizers of CYP2C9 substrates	Single dose	Complete [15Aug2005-03Oct2005]
CB8025-11733	5.3.4.1	Assess the effect of a single oral dose of seladelpar 10 or 200 mg on electrocardiogram parameters with a focus on cardiac repolarization compared to placebo	Single dose	Oral/ hard gelatin capsule=10 and 200 mg	60 planned 62 analyzed	Healthy male and female subjects	Single dose	Complete [21Dec2017-08Feb2018]

Reports of Efficacy and Safety Studies								
M8025-20711	5.3.5.1	Evaluate the absolute and percentage reduction of apolipoprotein B-100 (Apo B 100)	Multicenter, randomized, double-blind, placebo-controlled	Oral capsules/ 50 and 100 mg Atorvastatin= 20 mg	180 planned 183 randomized	Moderately obese hyperlipidemic subjects with or without concomitant atorvastatin	5 weeks	Complete [29Aug2007-13Aug2008]
CB8025-21528	5.3.5.1	Evaluate the percentage change from baseline to end-of-treatment in ALP level	Double-blind, randomized, placebo-controlled, phase 2 study	Oral capsules / 50 and 200 mg/day PO	75 planned 41 randomized	PBC	12 weeks	Complete [04Nov2015-01Jul2016]
CB8025-31735	5.3.5.1	Evaluate safety and efficacy	Placebo-controlled, randomized, phase 3 study	Oral capsules / 5 and 10 mg/day PO	240 planned 265 randomized	PBC	52 weeks	Complete [01Oct2008-16Feb2020]
CB8025-21730	5.3.5.1	Evaluate the safety, tolerability, and efficacy	Phase 2, double-blind, randomized, placebo-controlled study followed by open-label extension	Oral capsules / 10, 20, 50 mg/day PO	175 planned 181 randomized	NASH	52 weeks	Complete [27Apr2018-10Aug2020]
CB8025-32048	5.3.5.1	Evaluate the efficacy and safety of seladelpar in patients with PBC and an inadequate response to or an intolerance to ursodeoxycholic acid	A placebo-controlled, randomized, phase 3 study	Oral capsules 10 mg	180 planned 193 randomized	PBC	52 weeks	Complete [21Apr2021-11Aug2023]

CB8025-21427	5.3.5.2	Evaluate the absolute and percentage reduction in serum LDL-C	Open-label, dose-escalating, phase 2 study	Oral capsules/ 50, 100, and 200 mg/day PO	10 planned 13 randomized	HoFH	12 weeks	Complete [11Jun2015-15Feb2016]
CB8025-31731	5.3.5.2	Evaluate the long-term safety and tolerability	Phase ¾, open-label, long-term	Oral capsules/ 5 and 10 mg/day PO	350 planned 106 enrolled	PBC	5 years	Complete [11Dec2017-11Feb2020]
CB8025-31731-RE	5.3.5.2	Evaluate the safety and tolerability of seladelpar in subjects with PBC	An open-label long-term study	Oral capsules 10 mg	Up to 500 planned 280 subjects received at least 1 dose	PBC	5 years	Ongoing
CB8025-21629	5.3.5.2	Evaluate the safety, efficacy, and PK	Dose-ranging, open-label, randomized, phase 2 study, with a 44-week extension	Oral capsules/ 2, 5, and 10 mg/day PO	128 planned 119 enrolled	PBC	52 weeks	Complete [28Nov2016-08Jul2019]
CB8025-11941	5.3.5.2	To determine the effect of food on the PK of seladelpar after a single oral 10-mg dose under fed and fasted conditions in healthy subjects	Open-label, randomized 2-period, crossover study	Oral/ hard gelatin capsule=10 mg	16 planned 16 analyzed	Healthy male and female subjects	6 weeks	Complete [18Mar2022-27Mar22]

ALP=alkaline phosphatase; B=black; BA=bioavailability; BCRP=breast cancer resistance protein; CYP=cytochrome P450; F=female; HDL-C=high-density lipoprotein cholesterol; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; M=male; M1, M2, and M3=seladelpar metabolites; mg=milligram; ml=milliliter; NA=not applicable; NASH=non-alcoholic steatohepatitis; NC=not collected; O=other; OAT=organic anion transporter; PBC=primary biliary cholangitis; PD=pharmacodynamics; P-gp=P-glycoprotein; PK=pharmacokinetics; PO=oral; PPAR=peroxisome proliferator receptor; PSC=primary sclerosing cholangitis; W=white.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

A total of 19 clinical studies have contributed to the characterisation of the clinical pharmacology of seladelpar. Thirteen phase 1 studies have been conducted assessing seladelpar in healthy subjects, including 1 single ascending dose study at doses ranging from 1 to 360 mg that also explored food effect (NAP-1001), 1 multiple ascending dose study with doses ranging from 50 to 200 mg (NAP-1002), 4 DDI studies (NAP-1002, NAP-1003, NAP-1004, CB8025-11840), 1 single dose food effect study (CB8025-11941), 1 AME study (CB8025-11734), 1 TQT study (CB8025-11733;), and 2 relative bioavailability studies (CB8025-11836 and NAP-1005).

Additional phase 1 studies included 2 studies in subjects with varying degrees of hepatic impairment (1 in subjects with hepatic impairment due to a range of underlying liver diseases [Study CB8025-11732], and 1 in subjects with PBC and hepatic impairment [CB8025-21838]); and 1 study in subjects with renal impairment (CB8025-11942).

One phase 2 study was conducted in moderately obese subjects with hyperlipidaemia (M8025-20711 including interaction potential with atorvastatin), as well as one study in subjects with homozygous familial hypercholesterolemia (CB8025-21427).

Six studies conducted in subjects with PBC contributed to seladelpar pharmacokinetics (PK) and/or exposure-response (E-R) including Phase 1b study CB8025-21838 in subjects with PBC and hepatic impairment, Phase 2 study CB8025-21629 in subjects with PBC and inadequate response to UDCA, and Phase 3 studies CB8025-32048 (sparse PK only), CB8025-31735 (no PK), CB8025-31731 (no PK), and CB8025-31731-RE (sparse PK only).

A population PK (popPK) model was developed using 12 clinical pharmacology studies to evaluate the impact of intrinsic and extrinsic factors on the PK of seladelpar and the metabolite M2. The relationships between seladelpar exposure and efficacy/safety were evaluated in E-R analyses using exposure estimates from the popPK model. In addition, the PK and drug-drug interaction (DDI) potential of seladelpar was further evaluated using a physiologically based PK (PBPK) model.

A summary of PK results of seladelpar in Phase 1 and Phase 2 studies are shown in table below.

Table 2: Summary (mean ± SD) of seladelpar PK parameters in clinical pharmacology studies

Phase Study Number	**Seladelpar Dose**	**C_{max} (ng/mL)**	**AUC_{0-t} (h·ng/mL)**	**AUC_{∞} (h·ng/mL)**	**T_{max} (h)**	**$t_{1/2}$ (h)**
Phase 1						
NAP-1001	1 mg	4.40 ± 1.25	NR	NR	3.50 (0.670*, 6.00*)	NR
	5 mg	28.5 ± 3.59	340 ± 35.4	311 ± 69.7	1.75 (0.670*, 8.00*)	5.66 ± 0.910*
	15 mg	86.3 ± 25.9	621 ± 152	667 ± 148	2.00* (0.330*, 3.00*)	5.07 ± 1.11
	60 mg	795 ± 227	3930 ± 545	4130 ± 617	1.75 (1.02, 2.00*)	6.04 ± 1.35
	120 mg	2180 ± 805	6790 ± 1140	7030 ± 1200	1.00 (1.00*, 3.00*)	7.56 ± 1.15
	360 mg	9340 ± 2270	33,600 ± 5190	34,600 ± 5410	2.00* (0.330*, 4.00*)	8.26 ± 2.43
	120 mg fasted	3020 ± 1110	9550 ± 4780	10,100 ± 5340	1.50 (0.670*, 2.50)	9.91 ± 2.80
	120 mg fed	1280 ± 751	8760 ± 4000	9600 ± 4660	4.00 (1.50, 12.0)	9.71 ± 3.09
NAP-1002	50 mg/Day 1	496 ± 149	2370 ± 784	2460 ± 869	1.50 (0.670, 1.53)	5.03 ± 1.26
	100 mg/Day 1	1660 ± 655	5570 ± 1610	5750±1680	1.50 (0.670, 4.03)	5.03 ± 0.438
	200 mg/Day 1	3970 ± 2710	11,100 ± 3840	11300 ±3960	1.50 (1.00, 8.00)	4.43 ± 0.681
	50 mg/Day 21	436 ± 78.6	2720 ± 790	NA	0.670 (0.330, 1.50)	9.31 ± 4.54
	100 mg/Day 21	1390 ± 402	6810 ± 1950	NA	1.05 (0.230, 1.53)	11.5 ± 3.35
	200 mg/Day 21	3570 ± 1150	14,500 ± 5720	NA	1.50 (1.00, 1.52)	13.6 ± 1.40
NAP-1003	200 mg Seladelpar + 80 mg Simvastatin	6170 ± 2270	17,000 ± 4740	17,900 ± 5080	1.25 (0.500, 2.08)	7.89 ± 0.907
NAP-1004	500 mg Tolbutamide + 200 mg Seladelpar	3600 ± 1150	10,900 ± 2680	11,300 ± 2850	1.48 (0.330*, 4.00)	11.4 ± 4.30*
CB8025-11732	10 mg/Normal	71.9 ± 28.0	668 ± 217	705 ± 227	2.00* (0.500*, 4.00*)	6.66 ± 1.57
	10 mg/Mild HI	101 ± 58.7	785 ± 423	815 ± 432	1.50* (0.500*, 4.00*)	6.20 ± 1.75
	10 mg/Moderate HI	398 ± 199	1760 ± 606	1810 ± 612	1.00* (0.500*, 1.50*)	6.19 ± 1.37
	10 mg/Severe HI	379 ± 180	1570 ± 886	1620 ± 879	0.500* (0.500*, 4.00*)	7.21 ± 1.58
CB8025-11733	10 mg	87.5 ± 46.3	611 ± 354	647 ± 353	1.30* (0.500*, 4.00*)	4.96 ± 2.00

Phase Study Number	Seladelpar Dose	C_{max} (ng/mL)	AUC_{0-t} (h·ng/mL)	AUC_{∞} (h·ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
	200 mg	6160 ± 1790	17,100 ± 5820	17,200 ± 5830	1.60* (1.00*, 3.00*)	9.92 ± 2.50
CB8025-11734	10 mg	77.6 ± 29.2	595 ± 215	624 ± 219	1.50 (1.00, 4.00)	5.98 ± 1.49

Phase Study Number	Seladelpar Dose	C_{max} (ng/mL)	AUC_{0-t} (h·ng/mL)	AUC_{∞} (h·ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
Phase 1						
CB8025-11836	10 mg Neat Drug	92.4 ± 22.5	753 ± 274	780 ± 279	2.00 (0.500*, 4.00)	4.94 ± 1.25
	10 mg/Formulation 2	88.1 ± 28.5	746 ± 276	775 ± 279	2.00 (0.500*, 4.00)	5.02 ± 1.78
CB8025-11941	10 mg/Fasted	83.9 ± 31.4	730 ± 285	755 ± 291	3.48 (1.00, 8.12)	5.40 ± 1.89
	10 mg/Fed	56.1 ± 19.8	635 ± 222	671 ± 220	6.00 (3.98, 12.0)	6.21 ± 1.45
CB8025-11942	10 mg/Mild RI	85.6 ± 33.4	690 ± 204	726 ± 220	2.00 (0.500, 6.00)	4.81 ± 1.18
	10 mg/Moderate RI	85.8 ± 40.7	961 ± 511	1010 ± 557	2.75 (1.00, 10.0)	7.93 ± 3.04
	10 mg/Severe RI	86.8 ± 45.1	645 ± 422	694 ± 427	3.25 (1.00, 6.00)	5.85 ± 3.52
CB8025-21838	**Part A**					
	10 mg/Mild HI without PHT	182 ± 60.7	800 ± 214	841 ± 228	1.21 (0.500, 2.50)	4.53 ± 4.71
	10 mg/Mild HI with PHT	368 ± 238	1390 ± 504	1540 ± 474	0.758 (0.500, 6.00)	3.70 ± 0.246
	10 mg/Moderate HI	359 ± 159	1390 ± 812	1440 ± 829	1.25 (0.417, 3.00)	4.27 ± 0.838
	Part B					
	10 mg/Mild HI with PHT	299 ± 183	1450 ± 548	1480 ± 558	1.00 (1.00, 5.00)	4.21 ± 0.765
	10 mg/Moderate HI	344 ± 121	1030 ± 210	1060 ± 200	1.00 (0.467, 2.48)	4.23 ± 1.26
	5 mg/Mild HI with PHT (N = 1)	78.4	814	847	1.50	4.61
	5 mg/Moderate HI (N = 1)	229	1490	1560	0.500	5.36
Phase 2						
CB8025-21629	2 mg/Week 12	25.9 ± 16.5	71.0 ± 5.77	NA	2.48 (0.967, 4.00)	1.75**
	5 mg/Week 12	63.8 ± 35.7	207 ± 85.1	NA	3.58 (0.483, 6.00)	2.74 (0.548)
	10 mg/Week 12	97.3 ± 56.5	893 ± 394	NA	2.72 (1.00, 4.15)	6.72 (6.11)

AUC_{0-t} = area under the concentration versus time curve from time zero to the time of last quantifiable concentration; AUC_{∞} = area under the concentration versus time curve extrapolated to infinite time; C_{max} = maximum observed concentration of drug; HI = hepatic impairment; NA: not applicable; NR: not reported due to limited quantifiable concentrations; PHT = portal hypertension; RI = renal impairment; $t_{1/2}$ = terminal elimination half-life; T_{max} = time (observed time point) of C_{max}

* Less than three significant figures were reported in source data, and zeros were added to present the numbers as three significant figures.

** Standard deviation not provided as N = 1 for $t_{1/2}$ calculation.

Note: Mean (standard deviation) results are presented unless otherwise indicated. Median (minimum, maximum) is presented for T_{max}.

Source: 800025-NAP-1001 CSR; 800025-NAP-1002 CSR; 800025-NAP-1003 CSR; 800025-NAP-1004 CSR; CB8025-11732 CSR; CB8025-11733 CSR; CB8025-11734 CSR; CB8025-11836 CSR; CB8025-11941 CSR; CB8025-11942 CSR; CB8025-21838 CSR; CB8025-21629 CSR

Methods

Bioanalytical methods

Seladelpar concentrations in human plasma samples were analysed by validated LC-MS/MS methods.

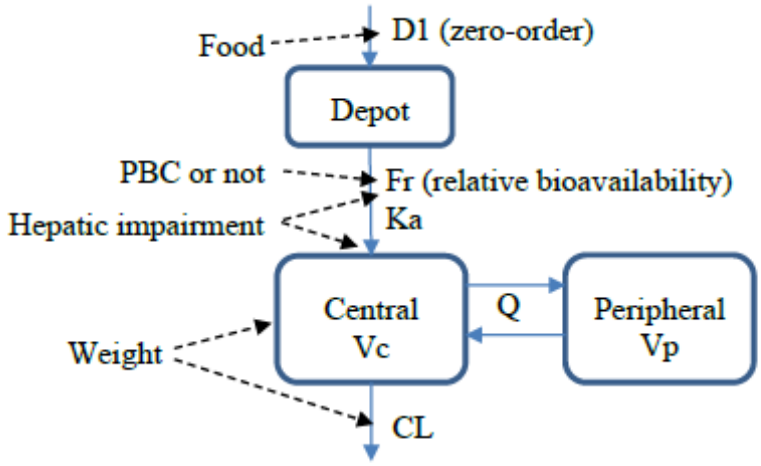
Population pharmacokinetic analysis

A nonlinear mixed effects modelling (i.e., popPK) analysis was conducted on pooled data from multiple studies, using validated software NONMEM v. 7.4.3. The objectives of the popPK analysis were to characterise the plasma PK of seladelpar, and to assess steady-state exposures and sources of variability in subjects with PBC. The popPK analysis was conducted on pooled PK data from 8 studies in healthy volunteers and 4 studies in subjects with PBC (CB8025-21838, CB8025-21629, CB8025-32048, and CB8025-31731-RE). Data from 488 subjects were included in the analysis, 275 (56%) of these were PBC patients. In total, 22% of the seladelpar measurements were below the lower limit of quantification (LLOQ). The initial concentration measurement below LLOQ (in the descending phase) was set to half LLOQ and kept in the analysis, while subsequent measurements below LLOQ were excluded from the analysis. There were in total 4781 concentration measurements of seladelpar included in the analysis, and 1950 (41%) of these measurements were from PBC patients.

The base model was a two-compartment distribution model with sequential zero-order (parameterised by duration [D1]) and first-order absorption (Ka). Random effects were estimated on both absorption parameters, both clearances (CL and Q), and both volumes of distribution (Vc and Vp), with correlation between clearance (CL) and central volume (Vc). Inter-occasion variability in Ka was also included for the PBC studies, as it was highly significant. In addition, inter-individual variability for intercompartmental clearance (Q), as well as the residual error, were markedly higher in the PBC studies and were therefore estimated separately.

Key covariate effects were included already in the base model (*Figure 2*): an effect of food on zero-order absorption duration, effects of study population (PBC patients vs. others) and different categories of hepatic impairment (HI) on relative bioavailability (Fr), effects on body weight on both CL and Vc, and an additional effect of HI in PBC patients on Vc.

Figure 2: Base model structure for the seladelpar population pharmacokinetic model. Dashed arrows represent covariate effects included in the base model. Solid arrows represent mass transfer



CL=clearance of central compartment; D1=zero-order release duration (into gut); Ka=first-order absorption rate; Q= intercompartmental clearance; Vc=central volume of distribution; Vp=peripheral volume of distribution. Clearances and volumes are apparent. Note Fr includes the fraction of drug escaping hepatic first-pass metabolism (F_h) before it arrives in the central compartment.

Additional covariate effects were assessed in a full covariate model. However, none of the additional covariates changed the predicted C_{max} or AUC at steady state by a factor of >1.25 (i.e., to <80% or >125%) compared to the reference case (using 5th and 95th percentiles for continuous covariates); hence, these covariates were not considered to have a clinically relevant effect on PK and were therefore not retained in the final model. Parameter estimates for the final seladelpar popPK model are shown in table below.

Table 3: Final model parameter estimates for seladelpar

	Fixed Effect		Random Effect			
Parameter	**Value**	**RSE**	**SD**	**(CV%)[a]**	**RSE**	**Shrinkage**
Apparent clearance (L/hr)	12.6	3.31%	0.390	(40.5%)	4.33%	6.81%
Apparent central volume (L)	84.4	3.66%	0.287	(29.3%)	5.77%	29.0%
Apparent intercompartmental clearance (L/hr)	0.93	7.46%	0.584	(63.7%)	10.8%	52.2%
Different random effect in above in PBC studies	--	--	0.363	(37.5%)	36.7%	83.4%
Apparent peripheral volume (L)	25.9	9.6%	0.584	*(63.7%)*	*10.8%*	*52.2%*
Zero-order release duration to depot, fasted/unknown (hr)	0.228	16.3%	1.75	(454%)	8.93%	46.0%
Zero-order release duration to depot, fed (hr)	6.87	14.6%	0.440	(46.3%)	42.2%	84.2%
First-order absorption rate (1/hr)[b]	1.28	7.39%	0.629	(69.7%)	20.6%	60.6%
Inter-occasion variability of above	--	--	1.10	(154%)	6.63%	*64.4%*
Weight exponent on clearance	0.750	(fixed)	--	--	--	--
Weight exponent on central volume	1.00	(fixed)	--	--	--	--
Bioavailability multiplier for all non-PBC subjects	0.853	4.10%	--	--	--	--
Bioavailability multiplier for CP-A HI, no PHT	1.13	6.4%	--	--	--	--
Bioav. multiplier for CP-A HI+PHT, 2 studies[c]	1.54	9.28%	--	--	--	--
Bioav. multiplier for CP-A HI+PHT, CB8025-21629[c]	0.839	14.3%	--	--	--	--
Bioavailability multiplier for CP-B HI, no PBC	3.34	9.30%	--	--	--	--
Bioavailability multiplier for CP-B HI with PBC	1.48	8.40%	--	--	--	--
Bioavailability multiplier for CP-C HI	2.45	6.71%	--	--	--	--
Central volume multiplier for HI, no PBC	1.00	(fixed)	--	--	--	--
Central volume multiplier for HI with PBC	0.789	5.4%	--	--	--	--
Clearance-central volume correlation	--	--	0.552	(59.7%)	10.2%	--
Proportional residual error in non-PBC studies	--	--	0.250	(25.4%)	0.647%	14.0%
Proportional residual error in PBC studies	--	--	0.479	(50.8%)	0.731%	16.5%

CP=Child-Pugh; HI=hepatic impairment; mod./adv.=moderate/advanced; PHT=Portal hypertension; PPI=proton pump inhibitor; RSE=relative standard error (standard error/estimate); SD=standard deviation.

[a] CV% is derived from SD: sqrt(exp(SD^2)-1) × 100%.
[b] Sequential zero-order release into the gut and first-order absorption from the gut is assumed.
[c] Separate multipliers were used for studies CB8025-21838 together with CB8025-31731-RE and for CB8025-21629.

Diagnostic (goodness-of-fit) plots for the full dataset and by study group (not shown) suggested a reasonable model fit. Prediction-corrected visual predictive checks (pcVPCs; *Figure 3* and Figure 4) also indicated a reasonable overall fit, with a minor underestimation of C_{max} and a slight overestimation of post-peak concentrations in PBC patients.

Figure 3: Prediction-corrected visual predictive checks by time after dose for the final seladelpar population pharmacokinetic model, stratified by study population

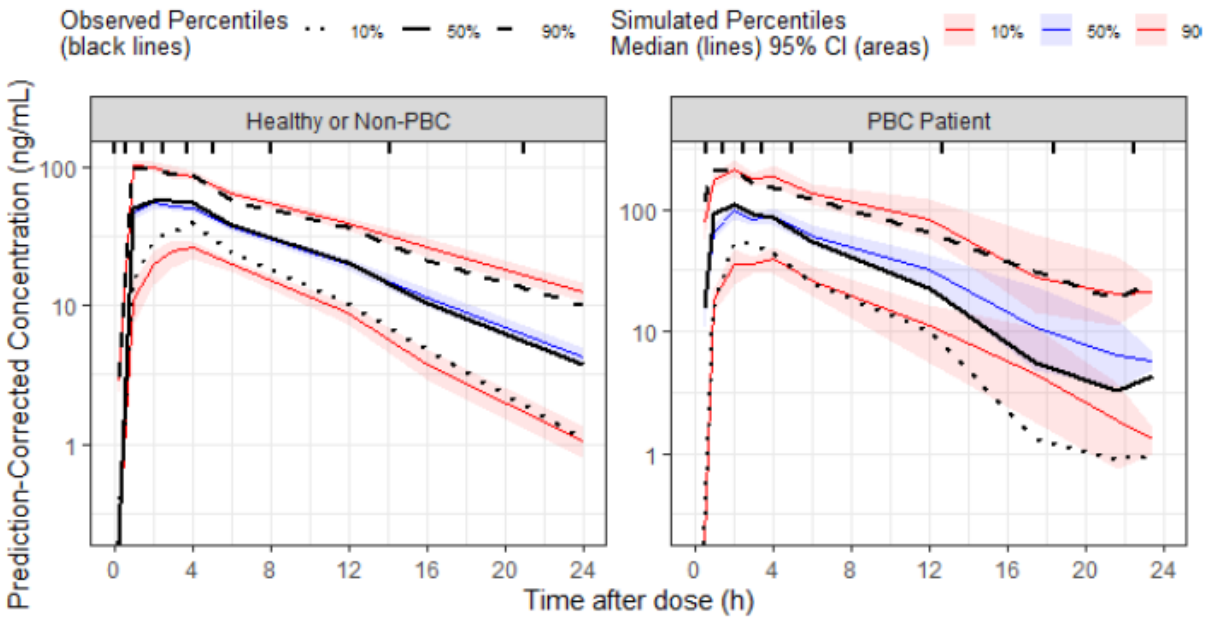
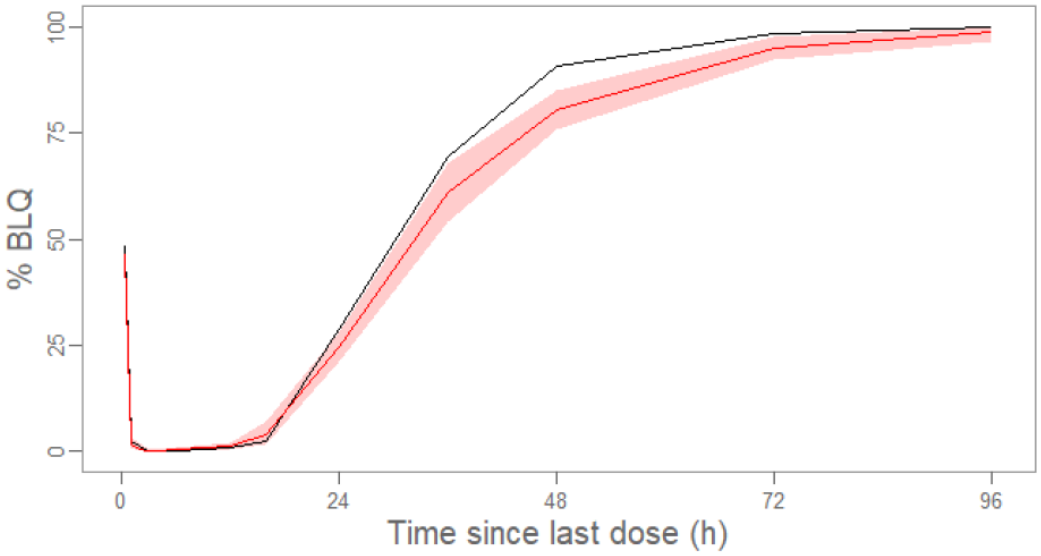
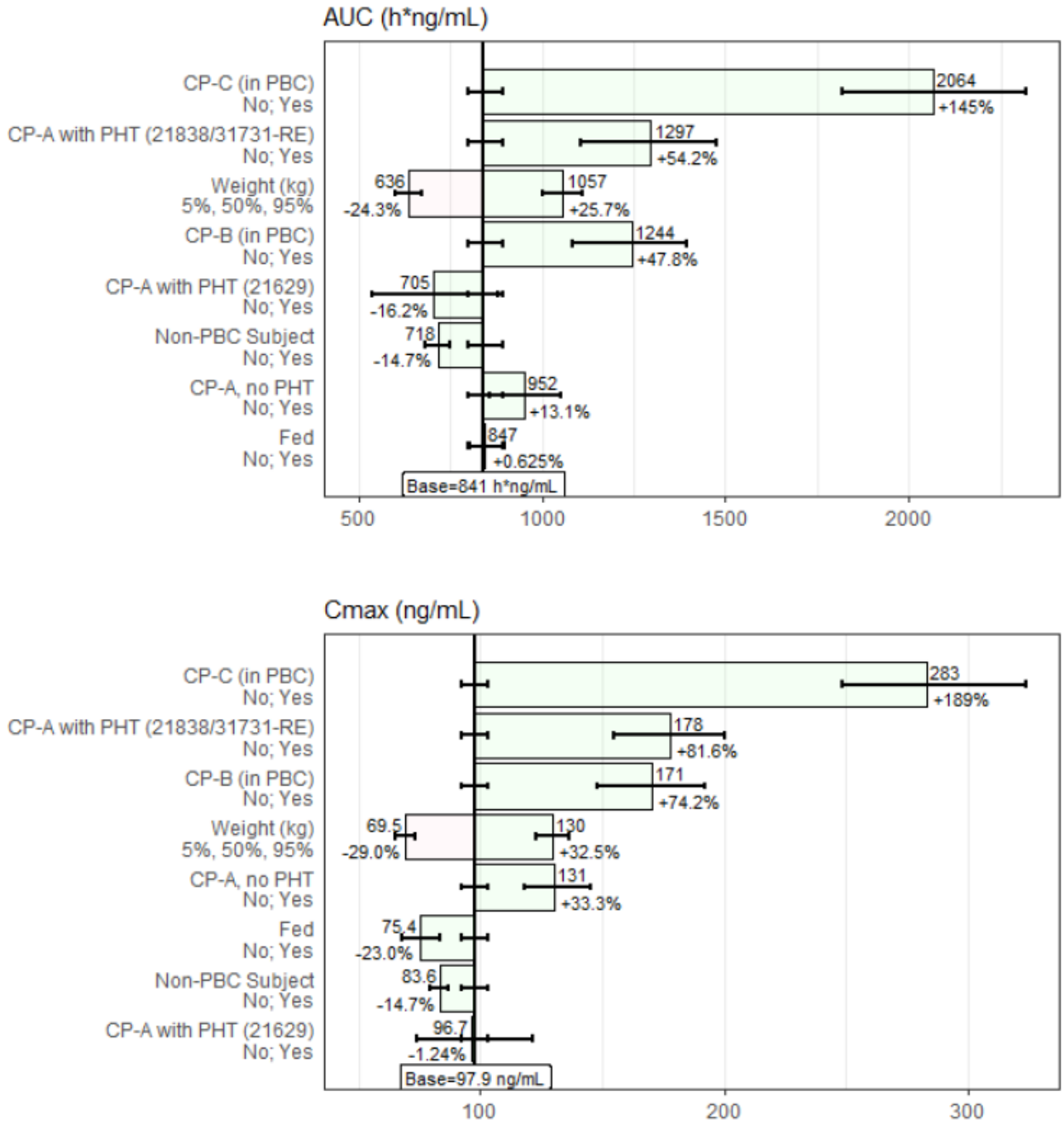


Figure 4: Visual predictive check of proportion of observations below limit of quantification (BLQ). The black line indicates observations, and the red line indicates predictions and the corresponding 95% CI



A sensitivity analysis tested the effects on steady-state exposure measures (AUC and C_{max}) of varying covariates one at a time, from median or reference values to 5th and 95th percentiles. This showed relatively large effects of moderate and severe HI, respectively (Child-Pugh B and C, respectively), as well as mild HI (Child-Pugh A) with portal hypertension (PHT), compared to the smaller effects (<26% for AUC) of variations from the typical subject (68.1-kg female PBC patient) based on body weight and food status.

Figure 5: The impact of different covariates on seladelpar steady-state exposure, relative to a typical PBC patient



Physiologically based pharmacokinetic analysis

A PBPK model was developed on the Simcyp platform (Simcyp Simulator v20 and v21).

A mechanistic oral absorption and metabolism PBPK model was developed for the to-be-marketed immediate-release (IR) capsule formulation of seladelpar, to evaluate clinically relevant dissolution specifications and to assess the risk for drug-drug interactions (DDIs). The model was developed using *in vitro* data including drug specific physiochemical properties, solubility, permeability, blood binding, and clinical data from Studies CB8025-11836 and CB8025-11840.

Two alternative absorption models were developed, an *in vitro* to *in vivo* extrapolation (IVIVE) based model and an *in vitro* to *in vivo* correlation (IVIVC) based model. For the IVIVE-based model, the *in vitro* dissolution data were modelled to derive the liberation rate of particles from the capsule product

as a first order disintegration rate constant (Kd). The Kd, along with particle size information, was used to capture the formulation impact *in vivo*. For the IVIVC-based model, the *in vitro* dissolution was assumed to represent *in vivo* dissolution in the GI tract. The absorption models were verified to predict the observed absorption following administration of the to-be-marketed IR capsule formulation (both models) and the drug substance in capsule (DSIC; only the IVIVE-based model), respectively. Using the IVIVE-based model, simulations were conducted to assess the impact of various liberation rates (i.e., Kd) on the PK of seladelpar. Using the IVIVC-based model, simulations were conducted to assess the impact of various hypothetical dissolution profiles on the PK of seladelpar, to identify the dissolution safe space.

The elimination part of the PBPK model was verified to predict the observed clinical DDI with fluconazole and then refined to further verify its ability to predict the observed DDI with carbamazepine. Based on the PBPK model, simulations were performed to understand the role of CYP2C9 versus CYP3A4 inhibition on seladelpar PK. Simulations were conducted to evaluate the interactions with strong, moderate, and weak CYP3A4 inhibitors, respectively, as well as strong CYP2C8 inhibitors.

Absorption

No absolute bioavailability study was conducted. The results from the oral mass balance study indicate that seladelpar is a compound with a high fraction absorbed, >85%, and hence a highly permeable compound. Adding 10% (M2 in faeces) and 2% (M12 in faeces) to the 73.4% excreted in urine, results in 85.4% as fraction absorbed in the mass balance study CB8025-11734 following oral administration.

Bioequivalence

Formulation development: The seladelpar drug substance is manufactured as a lysine dihydrate salt. The free acid is the active moiety, and the strength of the unit dose is based on the free acid (10 mg free acid is equivalent to 14.1 mg seladelpar lysine). Seladelpar drug substance has one stereogenic centre and is being developed as a single enantiomer of the R-configuration. The seladelpar formulations used in clinical studies are presented in *Table 4*. Initial clinical studies were performed utilising the neat drug substance in a bottle for reconstitution. DSIC (drug substance in capsule) was introduced to enable dosing at lower strengths in clinical studies. The drug product manufacturing process was further optimised, and Formulation 2 was developed. Formulation 2 was manufactured for the pivotal studies (Phase 3) and is the to-be-marketed formulation.

Table 4: Description of formulations used in clinical studies

	Solution	Formulation 1	DSIC	Formulation 2[a]
Formulation Description	Drug substance (neat) to be reconstituted with water	Formulated blend 1 in hard gelatin capsule	Drug substance (neat) in hard gelatin capsule	Formulated blend 2 in hard gelatin capsule (to-be-marketed formulation)
Seladelpar Capsule Strength	Not applicable. Powder in bottle	50 and 100 mg	1, 5, 10, and 25 mg	5 and 10 mg
Studies Using Formulation	NAP-1001, NAP-1002, NAP-1003, NAP-1004, NAP-1005	NAP-1005, CB8025-11733, MB8025-20711, CB8025-21427, CB8025-21528	CB8025-11732, CB8025-11733, CB8025-11836, CB8025-21629, CB8025-21730, CB8025-31731	CB8025-11836, CB8025-11840, CB8025-11941, CB8025-11942, CB8025-31735, CB8025-31731, CB8025-21838, CB8025-31731-RE, CB8025-32048

Abbreviations: DSIC = drug substance in capsule
[a] Seladelpar drug product; represents the to-be-marketed formulation

Two relative bioavailability studies were submitted: study NAP-1005 comparing Solution and Formulation 1 and study CB8025-11836 comparing DSIC and Formulation 2 (to-be-marketed solution). The two capsule formulations DSIC and Formulation 2 (= to-be-marketed formulation) have similar relative bioavailability of seladelpar. Also, the two early formulations (solution and Formulation 1) have similar relative bioavailability of seladelpar.

Food interaction

The effect of food on systemic exposure to seladelpar was studied by assessing the PK of a single dose of seladelpar in 2 crossover studies (NAP-1001 and CB8025-11941) in healthy adult subjects under fasting and fed conditions. The first study (NAP-1001) was conducted using the initial formulation (drug substance in oral solution) whereas the second study (CB8025-11941) was conducted using to-be-marketed formulation.

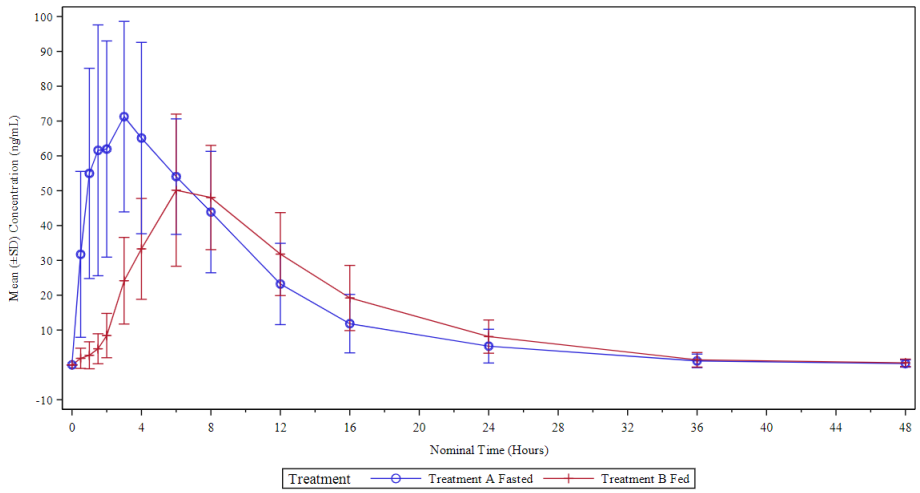
Both studies resulted in comparable AUC of seladelpar and its metabolites following administration in fasted and fed state. The C_{max} of seladelpar was reduced and the t_{max} delayed in fed compared to fasted conditions. Following administration of the to-be-marketed formulation C_{max} values of seladelpar was reduced by approximately 32% and seladelpar t_{max} was delayed by approximately 2.5 hours in fed conditions compared to fasted conditions.

The results of study CB8025-11941 are shown below.

Table 5: Statistical analysis of food effect (fed vs fasted) in study CB8025-11941

Analyte	Comparison	Parameter (unit)	Geometric LSM		Ratio (Fed/Fasted)[1]	90% C.I.[2]	
			Fed	Fasted		Lower	Upper
MBX-8025(seladelpar)	Fed vs Fasted	AUC_{0-t} (h*ng/mL)	604.34	689.37	87.67	81.85	93.89
		AUC_{0-inf} (h*ng/mL)	641.02	714.30	89.74	83.93	95.95
		C_{max} (ng/mL)	53.91	78.76	68.45	59.65	78.55

Figure 6: Mean (±SD) plasma concentrations of seladelpar by treatment - linear scale (study CB8025-11941)



Distribution

In single-dose studies in healthy subjects, values of V/F of 93-157 L have been reported. In the popPK analysis, a V/F at steady state of 110 L was suggested.

The plasma protein binding of seladelpar was 99.7% in human plasma throughout the concentration range of 2000 to 20000 ng/mL using equilibrium dialysis. At 200 ng/mL, the protein binding was estimated to >99.5%, and a more precise value could not be calculated due to that LOQ was 1.00 ng/mL. The plasma protein binding was not concentration dependent. A high degree of binding to albumin and AAG, >99%, was seen for seladelpar.

In the mass balance study CB8025-11734, the mean blood/plasma total radioactivity AUC ratio was 0.534, indicating low association of radioactivity with red blood cells.

Elimination

In the popPK analysis typical PBC-subject clearance was 13 L/h for seladelpar.

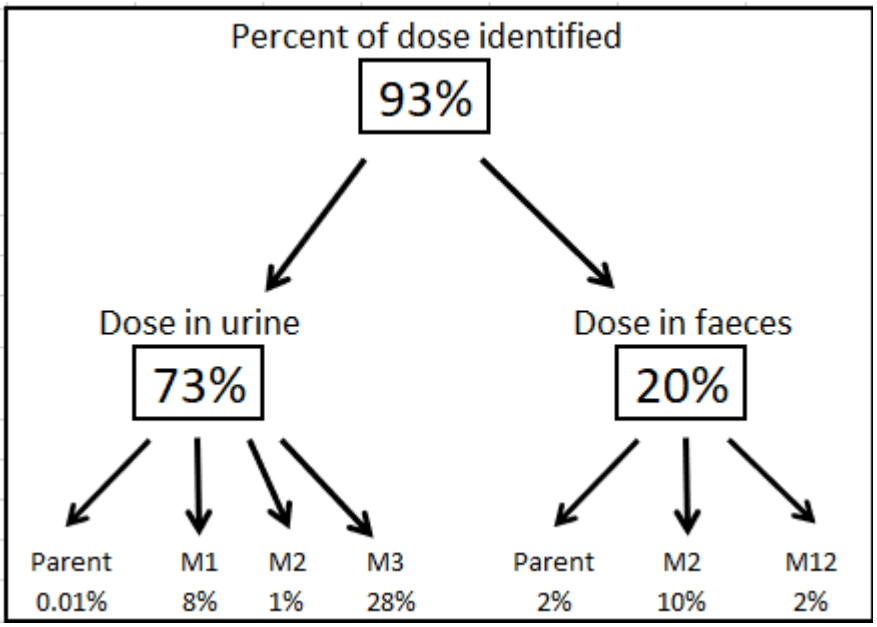
The plasma half-life of seladelpar ranged from 5-7 hours in healthy subjects following a dose of 10 mg.

Mass balance

The mass balance study CB8025-11734 was a single dose study with an oral dose of 10 mg/100 µCi (3.7 MBq) [14C]-seladelpar administered to eight healthy subjects (4 males and 4 females) under fasting conditions. The results of the mass balance study are summarised in *Figure 7*.

The majority (73.4%) of the radioactivity was excreted in urine and a smaller part (19.5%) in faeces. The overall mean recovery of radioactive dose in all excreta (urine and faeces) over 216 hours was approximately 92.9%. Most of the radioactivity in both urine and faeces was in the form of metabolites. Less than 0.01% of the dose was excreted as unchanged drug in urine. In faeces, 2% of the dose was recovered as unchanged seladelpar. Excretion parameters for total radioactivity were comparable between females and males.

Figure 7: Mass balance results



Metabolism

In vitro:

The main metabolites identified following incubations in human liver microsomes and human S9 fractions were M1 (sulfoxide metabolite) and M2 (O-dealkylated metabolite). These metabolites were also found in large amounts *in vivo* together with M3. The results of *in vitro* phenotyping study No. MC20M-0064 showed that M1 was formed primarily by 2C8 with additional contributions in the order of 3A4>2C9. M2 was generated predominantly by 2C9 with minor formation by 2C8. M3 was produced predominantly by 2C9 with minor contribution from 2C8, 3A4 and possibly 2C19.

In vivo:

The pharmacokinetic results of seladelpar and total radioactivity in plasma and blood in study CB8025-11734 are shown in Table 7. Mean t½ was 6 hours for seladelpar, 133 hours for total radioactivity in plasma and 30 hours for total radioactivity in whole blood.

Seladelpar was not a major contributor to the circulating plasma total radioactivity, accounting for 8.11% of the circulating total radioactivity in plasma. The 3 main metabolites accounted for 25.54% (3.02% for M1, 17.6% for M2, and 4.92% for M3) of the total plasma radioactivity.

Table 6: Summary of the pharmacokinetic parameters for seladelpar in plasma and total radioactivity in plasma and whole blood (study CB8025-11734)

Parameter	Plasma Seladelpar (N=8)	Plasma Total [^{14}C] Radioactivity (N=8)	Whole Blood Total [^{14}C] Radioactivity (N=8)
C_{max} (ng/mL or ng equiv/g)	72.9 (39.5)	249 (30.0)	142 (34.2)
t_{max} (h)	1.50 (1.00, 4.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)
AUC_{0-t} (h*ng/mL or h*ng equiv/g)	561 (38.1)	7040 (27.2)[a]	2930 (52.8)[a]
$AUC_{0-\infty}$ (h*ng/mL or h*ng equiv/g)	591 (36.8)	NA	2670 (41.9)[b]
$t_{1/2}$ (h)	5.98 (1.49)	133 (17.0)[c]	29.9 (18.4)[b]
CL/F (L/h)	18.1 (36.8)	NA	NA
V_z/F (L)	152 (33.1)	NA	NA
Plasma Seladelpar/Total Radioactivity AUC Ratio	0.0811 (20.8)	NA	NA
Blood/Plasma Total Radioactivity AUC Ratio	NA	NA	0.534 (9.40)

Source: Table 14.2.1-1
Abbreviations: AUC = area under the concentration-time curve; AUC_{0-t} = AUC from time 0 to the time of the last quantifiable concentration; $AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; CL/F = apparent total clearance; C_{max} = maximum observed concentration; N = number of subjects; NA = not applicable; NC = not calculated; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of maximum observed concentration; V_z/F = apparent volume of distribution during the terminal elimination phase.
Note: Geometric mean (geometric coefficient of variation) results are presented unless otherwise indicated. Median (minimum,maximum) is presented for t_{max}. Arithmetic mean (standard deviation) results are presented for $t_{1/2}$.
[a] N = 7; [b] N = 4; [c] N = 3

Table 7: Summary of the pharmacokinetic parameters of seladelpar metabolites M1, M2, and M3 in plasma (study CB8025-11734)

Parameter	Plasma M1 (N=8)	Plasma M2 (N=8)	Plasma M3 (N=8)
C_{max} (ng/mL)	12.7 (33.6)	91.5 (40.9)	26.2 (25.7)
t_{max} (h)	10.00 (6.00, 10.00)	4.00 (1.50, 6.00)	4.00 (4.00, 8.00)
AUC_{0-t} (h*ng/mL)	194 (43.6)	1100 (59.4)	319 (38.8)
$AUC_{0-\infty}$ (h*ng/mL)	225 (39.6)[a]	1320 (52.4)[a]	369 (35.3)[a]
$t_{1/2}$ (h)	9.61 (1.70)	10.3 (2.85)[a]	9.01 (1.64)[a]
MR_{AUC}	0.359 (14.4)	2.32 (24.4)[a]	0.625 (18.1)[a]
Plasma Metabolite/Total Radioactivity AUC Ratio	0.0302 (27.1)	0.176 (30.5)[a]	0.0492 (12.8)[a]

Source: Table 14.2.1-1
Abbreviations: AUC = area under the concentration-time curve; AUC_{0-t} = AUC from time 0 to the time of the last quantifiable concentration; $AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; MR_{AUC} = metabolite-to-parent $AUC_{0-\infty}$ ratio; N = number of subjects; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of maximum observed concentration.
Note: Geometric mean (geometric coefficient of variation) results are presented unless otherwise indicated. Median (minimum, maximum) is presented for t_{max}. Arithmetic mean (standard deviation) results are presented for $t_{1/2}$.
[a] N = 7

Seladelpar was extensively metabolised following an oral dose of 14C-seladelpar with 13 identified and characterised metabolites and additional five quantified, but not structurally characterised metabolites in plasma, urine and faeces (Figure 8 and Table 9). Primary metabolism of seladelpar was mediated by oxidation and oxidative O-dealkylation. Secondary metabolism included oxidation, glucuronidation, and, to a lesser extent, sulfonation.

CYP2C9 is considered the major metabolic pathway of seladelpar, and this enzyme is polymorphic. The metaboliser status based on CYP2C9 polymorphisms was evaluated in 4 phase 1 studies to determine if individual genotypes affect the PK of seladelpar (Report CYMA-PGX-SELADELPAR-10162023). Only one poor metaboliser was identified. The present results showed similar Cmax and 18% increase in AUC∞ when comparing intermediate metaboliser versus normal metaboliser but no conclusion could be made for poor metabolisers due to too few individuals. The plasma exposure in the one identified poor

metaboliser in study 11840 was approximately doubled compared to mean AUC/dose in normal metabolisers. This subject was assigned the CYP2C9 phenotype *3/*2.

Figure 8: Proposed biotransformation pathways of seladelpar in humans

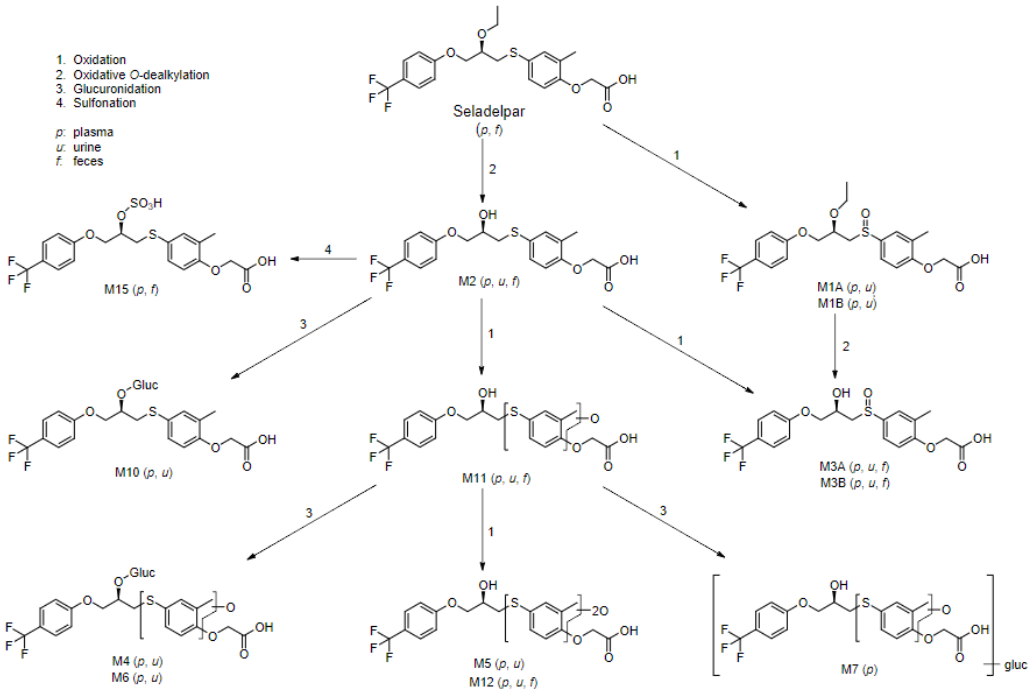


Table 8: Summary of metabolites

Component Designation	Retention Time (Minutes)	Proposed Identification	Matrix		
			Plasma	Urine	Feces
M4	14.00-14.33	desethyl-oxy-seladelpar glucuronide	X	X	
M5	14.00-14.33	desethyl-dioxy-seladelpar	X	X	
M6	14.83-15.00	desethyl-oxy-seladelpar glucuronide	X	X	
M7	15.83-16.33	desethyl-oxy-seladelpar glucuronide	X		
M8	17.33-17.50	unidentified			X
M3A	19.00	desethyl-seladelpar sulfoxide	X	X	X
M3B	19.67	desethyl-seladelpar sulfoxide	X	X	X
M9	20.67	unidentified	X		
M10	21.33-21.50	desethyl-seladelpar glucuronide	X	X	
M11	21.33-21.50	desethyl-oxy-seladelpar	X	X	X
M12	22.83-23.00	desethyl-dioxy-seladelpar	X	X	X
M1A	26.67-26.83	seladelpar sulfoxide	X	X	
M1B	27.33-27.50	seladelpar sulfoxide	X	X	
M2	28.67	desethyl-seladelpar	X	X	X
M13	30.17-30.33	unidentified			X
M14	31.00	unidentified			X
Seladelpar	38.17-38.33	Parent	X		X
M15	35.00-39.33	desethyl-seladelpar sulfate	X		X
M16	39.50-39.67	unidentified	X		

Notes: Retention time ranges are from profiling analyses of all matrices.
Metabolite found in matrix designated with "X".

There is one major metabolite in plasma, M2, which accounted for 17.6% of the total plasma radioactivity. The metabolite M2 has some PPARdelta activity but low compared to seladelpar (approximately 131-175 times lower) and M2 is not estimated to contribute to efficacy *in vivo*.

Dose proportionality and time dependencies

Dose proportionality

The plasma exposure (AUC and C_{max}) increased approximately proportional to dose from 2 mg to 15 mg. At higher doses, up to 360 mg, the AUC increased slightly more than proportional to dose and the increase in C_{max} was larger than dose proportional. Dose proportionality was evaluated from three studies (CB8025-21629, NAP-1001 and NAP-1002), see results below.

Time dependency

No major time dependency in the PK of seladelpar was observed. In study CB8025-21629 following 2-10 mg/day in PBC subjects, AUC and C_{max} was in the same range after 2 and 12 weeks of dosing compared to baseline, see Table 10. Also, in study NAP-1002 following 50-200 mg/day in healthy volunteers, AUC and C_{max} was in the same range day 1, 14 and 21, see below.

Table 9: Plasma pharmacokinetic parameters of seladelpar, M1, M2 and M3 after multiple oral doses of 2, 5 and 10 mg/day in subjects with PBC (study CB8025-21629)

Visit	Initial Dose[a]		Analyte							
			Seladelpar		M1		M2		M3	
			C_{max} (ng/mL)	AUC (ng•hr/mL)	C_{max} (ng/mL)	AUC (ng•hr/mL)	C_{max} (ng/mL)	AUC (ng•hr/mL)	C_{max} (ng/mL)	AUC (ng•hr/mL)
Visit 2 (Baseline)	2 mg (N = 5)	n	5	5	5	5	5	5	5	5
		Value	24.900 (14.424)	86.4365 (22.6585)	3.762 (1.037)	29.0364 (22.7174)	28.40 (10.37)	108.1558 (39.4741)	6.356 (2.030)	21.0052 (7.7848)
	5 mg (N = 12)	n	12	12	12	12	12	12	12	12
		Value	55.742 (26.146)	334.8960 (266.4902)	7.763 (3.753)	82.8040 (35.3610)	88.35 (32.62)	1066.6123 (361.3848)	13.133 (5.509)	134.9338 (74.5738)
	10 mg (N = 11)	n	11	11	11	11	11	11	11	11
		Value	138.745 (83.982)	645.7259 (350.4414)	21.036 (5.722)	211.4110 (54.8679)	158.94 (61.28)	1645.6616 (774.1669)	31.436 (10.565)	342.3596 (91.9246)
Visit 4 (Week 2)	2 mg (N = 5)	n	3	2	3	2	3	2	3	2
		Value	19.200 (18.674)	129.9360 (63.6118)	3.657 (3.493)	62.7756 (67.2821)	28.87 (30.57)	511.9537 (557.7960)	5.437 (4.719)	74.9710 (69.5030)
	5 mg (N = 12)	n	6	6	6	6	6	6	6	6
		Value	68.333 (20.811)	539.4430 (240.7595)	16.600 (12.574)	206.3777 (113.6618)	133.77 (72.44)	1869.6873 (815.4008)	18.145 (9.663)	272.5712 (143.7728)
	10 mg (N = 11)	n	4	4	4	4	4	4	4	4
		Value	155.250 (50.599)	1094.7421 (321.2468)	33.300 (13.152)	407.4070 (236.1549)	236.75 (35.29)	3444.9888 (782.2633)	44.050 (19.024)	710.4767 (373.9611)
Visit 8 (Week 12)	2 mg (N = 5)	n	2	2	2	2	2	2	2	2
		Value	25.850 (16.476)	70.9842 (5.7713)	3.855 (0.403)	42.7739 (37.5791)	26.65 (4.17)	108.8804 (11.4381)	6.825 (0.035)	64.9869 (49.0058)
	5 mg (N = 12)	n	6	6	6	6	6	6	6	6
		Value	63.777 (35.746)	207.3766 (85.0913)	11.810 (3.516)	140.4953 (39.3561)	98.60 (32.14)	1134.8149 (215.2258)	19.383 (4.954)	248.5890 (90.7926)
	10 mg (N = 11)	n	6	6	6	6	6	6	6	6
		Value	97.267 (56.515)	892.9767 (393.6686)	27.567 (8.059)	470.5616 (190.4797)	194.82 (107.04)	3116.1008 (1896.6656)	41.367 (10.627)	788.9592 (453.1030)

AUC = area under the time-concentration curve; C_{max} maximum plasma concentration; M = metabolite; mITT = modified intent-to-treat; n = number in category; N = number in treatment group; NE = not estimable; PK = pharmacokinetic; SD = standard deviation.

[a] Analysis is based on initial dose (subjects were enrolled to 2 mg or randomized to 5 mg or 10 mg). Beginning at the Week 12 visit, the initial dose could have been up- or down-titrated.

For Subject [redacted] (2 mg dose), the 24-hr time point at Week 12 was excluded.

Concentration values of 0 indicate measurements that were below the quantification level.

Therapeutic window

The applicant defines the upper bound of the therapeutic window as 2-fold of median steady state seladelpar exposure (C_{max} and AUC) following 10 mg once daily doses of seladelpar in PBC subjects. The lower bound of the therapeutic window is defined as 2-fold lower than the median exposure (C_{max} and AUC) of seladelpar following 10 mg once daily doses of seladelpar in subjects with PBC.

Special populations

Elderly

Table 10: Number of elderly subjects in pharmacokinetics studies (PK datasets)

	Age 65-74 (Older Subjects Number/Total Number[a])	**Age 75-84 (Older Subjects Number/Total Number[a])**	**Age 85+ (Older Subjects Number/Total Number[a])**
CB8025-11732	4/32	0/32	0/32
CB8025-11733	0/28	0/28	0/28
CB8025-11734	0/8	0/8	0/8
CB8025-11836	1/16	0/16	0/16
CB8025-11840	1/91	0/91	0/91
CB8025-11941	0/16	0/16	0/16
CB8025-11942	12/36	2/36	0/36
CB8025-21427	1/13	1/13	0/13
CB8025-21528	4/24	0/24	0/24
CB8025-21629	9/29	1/29	0/29
CB8025-21838	2/18	1/18	0/18
CB8025-31731-RE	19/81	2/81	0/81
CB8025-32048	17/71	2/71	0/71
M8025-20711	13/50	0/50	0/50
RWJ-800025-NAP-1001	0/26	0/26	0/26
RWJ-800025-NAP-1002	0/39	0/39	0/39

Table 11: Number of elderly subjects in pharmacokinetics studies (PK datasets) (continued)

	Age 65-74 (Older Subjects Number/Total Number[a])	**Age 75-84 (Older Subjects Number/Total Number[a])**	**Age 85+ (Older Subjects Number/Total Number[a])**
RWJ-800025-NAP-1003	0/12	0/12	0/12
RWJ-800025-NAP-1004	0/15	0/15	0/15
Total[b]	83/605	9/605	0/605

PK = pharmacokinetic

[a] Denominators are numbers of subjects with PK concentration of Seladelpar.

[b] Subjects in multiple pharmacokinetics studies were counted multiple times in the "Total" row.

Source: EU-Q70 Table 1

Impaired renal function

A renal impairment study was performed in patients with mild (eGFR ≥ 60 to < 90 mL/min), moderate (eGFR ≥ 30 to < 60 mL/min) and severe (eGFR < 30 mL/min and not on dialysis) renal impairment

and the PK following an oral single dose of 10 mg seladelpar was compared with matched healthy subjects with normal renal function (eGFR ≥ 90 mL/min). No ESRD patients on dialysis were included.

The results in plasma showed similar exposure in patients with severe renal impairment compared to matched normal controls, see *Table 12*. In patients with mild and moderate renal impairment, an increase in AUC (48% and 33%, respectively) was noted.

In the study CB8025-11942, the plasma protein binding of seladelpar was determined at 2.5 and 12 hours. The geometric mean fu of seladelpar across different renal function groups ranges from 0.270% to 0.302%, compared with 0.175% to 0.217% in the matched normal subjects.

Table 12: Comparison of total seladelpar AUC and C_{max} in subjects with RI to matched normal controls (assignment based on absolute eGFR), study CB8025-11942

Total Seladelpar Group Comparison	Parameter	Geometric LSM Ratios (90% CI)		
		Ratio (%)	Lower 90%CI	Upper 90%CI
Mild RI (N = 7) vs Matched Normal (N = 7)	AUC_{0-t} (h·ng/mL)	154	138	172
	AUC_{∞} (h·ng/mL)	148	136	161
	C_{max} (ng/mL)	117	68.7	199
Moderate RI (N = 7) vs Matched Normal (N = 7)	AUC_{0-t} (h·ng/mL)	134	89.9	200
	AUC_{∞} (h·ng/mL)	133	76.7	231
	C_{max} (ng/mL)	95.1	69.5	130
Severe RI (N = 6) vs Matched Normal (N = 6)	AUC_{0-t} (h·ng/mL)	96.7	62.0	151
	AUC_{∞} (h·ng/mL)	103	59.5	178
	C_{max} (ng/mL)	105	57.9	189

AUC = area under the concentration versus time curve; AUC_{∞} = area under the concentration versus time curve extrapolated to infinite time; AUC_{0-t} = area under the concentration versus time curve from time zero to time t; CI = confidence interval; C_{max} = maximum observed concentration of drug; eGFR = estimated glomerular filtration rate; LSM =least squares means; N = total number of subjects; RI = renal impairment; SE = standard error

Impaired hepatic function

Two hepatic impairment studies have been performed, one in subjects with varying degrees of HI (study CB8025-11732) and one in patients with PBC with varying degrees of HI (study CB8025-21838). Study CB8025-21838 is partly completed and still ongoing in patients with severe hepatic impairment.

Study CB8025-11732 was a parallel-group single-dose study following oral doses of 10 mg seladelpar in subjects with varying degrees of hepatic function and the pharmacokinetic results are shown in table below. Seladelpar exposure (AUC_{0-t} or AUC_{0-inf}) more than doubled (2.1-2.6-fold increase) and C_{max} increased 5-fold in subjects with moderate or severe HI compared to subjects with normal hepatic function. Exposure to seladelpar was generally similar in subjects with mild HI compared to normal subjects.

Table 13: Summary (arithmetic mean ± SD) of PK parameters for seladelpar in subjects with varying degrees of hepatic impairment (population: PK analysis set in study CB8025-11732).

PK Parameter	Cohort 1 Normal N=8	Cohort 2 Mild HI N=8	Cohort 3 Moderate HI N=8	Cohort 4 Severe HI N=8
C_{max} (ng/mL)	71.9 ± 28.0	101 ± 58.7	398 ± 199	379 ± 180
T_{max}[a] (hr)	2.0 (0.50, 4.0)	1.5 (0.50, 4.0)	1.0 (0.50, 1.5)	0.50 (0.50, 4.0)
AUC_{0-t} (hr*ng/mL)	668 ± 217	785 ± 423	1763 ± 606	1570 ± 886
AUC_{0-inf} (hr*ng/mL)	705 ± 227	815 ± 432	1807 ± 612	1616 ± 879
$t_{1/2}$ (hr)	6.66 ± 1.57	6.20 ± 1.75	6.19 ± 1.37	7.21 ± 1.58
CL/F (L/hr)	15.4 ± 4.45	14.3 ± 4.92	6.34 ± 3.00	7.78 ± 3.52
Vz/F (L)	141 ± 29.0	120 ± 36.5	54.6 ± 21.2	78.7 ± 30.6

Source: Table 14.2.2.1
a. T_{max} is presented as median (minimum, maximum).

Study CB8025-21838 was a 2-part, single (Part A) and multiple (Part B) oral dose study of ≤ 10 mg seladelpar in PBC subjects with cirrhosis and varying levels of hepatic impairment as determined by Child-Pugh classification. Subjects with Child-Pugh A were enrolled in 2 separate groups (i.e., those without and with evidence of PHT). The following groups were included; Cohort 1 (Child-Pugh A without PHT), cohort 2 (Child-Pugh A with PHT) and cohort 3 (Child-Pugh B) Enrolment for Cohort 4 (Child-Pugh C) is ongoing and not reported here. Part B (multiple dose) was limited to Cohort 2 and Cohort 3 subjects.

The pharmacokinetic results of study CB8025-21838 are presented in Table 14 and Table 15. The presence of PHT in subjects with CP-A (Cohort 2) resulted in exposures that were 71-83% higher than in subjects with CP-A without PHT (Cohort 1). Seladelpar exposure in Cohort 3 (CP-B) was approximately 57-89% higher than exposure in Cohort 1.

The plasma protein binding was evaluated at 2.5 and 12 hours in this study and the results of fu was 0.199% in Cohort 1 (CP-A without PHT), 0.303% in Cohort 2 (CP-A with PHT) and 0.283% in Cohort 3 (CP-B). This is similar as previously reported *in vitro* protein binding of >99.5 - 99.7% (fu <0.5% - 0.3%) and using total plasma PK parameters in the evaluation of this study is considered acceptable.

The results of the urine data showed a minor increase in renal clearance (CL_r) of seladelpar in Cohort 2 (0.004 L/h) and Cohort 3 (0.006 L/h) compared to Cohort 1 (0.002 L/h).

No evidence of meaningful drug accumulation was observed for 10 mg seladelpar following 28 days of administration in either Cohort 2 (CP-A with PHT) or Cohort 3 (CP-B).

Table 14: Summary (arithmetic mean [standard deviation]) of pharmacokinetic parameters of seladelpar - part A (single dose of seladelpar 10 mg) (pharmacokinetic analysis set)

Pharmacokinetic Parameter	**Cohort 1 (CP-A Without PHT) (N = 6)**	**Cohort 2 (CP-A With PHT) (N = 6)**	**Cohort 3 (CP-B) (N = 6)**
C_{max} (ng/mL)	182.0 (60.68)	367.7 (238.28)	359.2 (158.61)
T_{max} (h)	1.208 (0.500, 2.500)	0.758 (0.500, 6.000)	1.250 (0.417, 3.000)
AUC_{0-t} (h*ng/mL)	800.138 (213.9055)	1392.837 (504.4413)	1390.897 (811.5938)
AUC_{0-inf} (h*ng/mL)	841.247 (228.4063)	1535.878 (473.5249) [a]	1439.612 (829.4304)
$t_{1/2}$ (h)	4.5332 (4.70935)	3.7036 (0.24598) [a]	4.2682 (0.83795)
CL/F (L/h)	12.667 (3.6305)	6.920 (1.6876) [a]	8.637 (3.9444)
V_z/F (L)	68.977 (48.5108)	37.248 (10.3771) [a]	50.427 (17.7346)

Abbreviations: AUC = area under the concentration-time curve; AUC_{0-inf} = AUC from time 0 to infinity; AUC_{0-t} = AUC from time 0 to the time of last measurable concentration; CL/F = apparent clearance; C_{max} = maximum observed plasma concentration; CP = Child-Pugh; HI = hepatic impairment; n = number of subjects included in the analysis; PHT = portal hypertension;

Table 15: Summary (arithmetic mean [standard deviation]) plasma pharmacokinetic parameters for seladelpar – part B (pharmacokinetic analysis set

Day	Pharmacokinetic Parameter	Seladelpar 10 mg		Seladelpar 5 mg	
		Cohort 2 (CP-A With PHT) (N = 5)	Cohort 3 (CP-B) (N = 5)	Cohort 2 (CP-A With PHT) (N = 1)	Cohort 3 (CP-B) (N = 1)
Day 1	C_{max} (ng/mL)	299.08 (182.985)	344.40 (121.049)	78.40	229.00
	T_{max} (h)	1.0000 (1.000, 5.000)	1.0000 (0.467, 2.483)	1.500	0.5000
	AUC_{0-24} (h*ng/mL)	1449.502 (548.4039)	1052.746 (191.0524)	814.160	1494.424
	AUC_{0-t} (h*ng/mL)	1449.502 (548.4039)	1027.556 (209.6552)	814.160	1494.424
	AUC_{0-inf} (h*ng/mL)	1478.284 (557.7591)	1061.664 (199.7324)	846.662	1560.469
	$t_{1/2}$ (h)	4.2063 (0.76505)	4.2330 (1.25554)	4.6071	5.3605
	CL/F (L/h)	7.805 (3.7153)	9.695 (1.8401)	11.811	6.408
	V_z/F (L)	49.388 (33.135)	58.367 (17.9294)	78.504	49.559
Day 28	$C_{max\ ss}$(ng/mL)	260.60 (75.255)	324.00 (153.498)	53.20	255.00
	$T_{max\ ss}$ (h)	1.000 (0.500, 2.000)	0.5667 (0.500, 1.500)	3.5000	1.0333
	AUC_{0-24} (h*ng/mL)	1328.772 (516.8052)	1054.646 (380.1256)	570.133	1679.877
	AUC_{0-t} (h*ng/mL)	1401.888 (510.7965)	1069.926 (398.6305)	641.413	1679.877
	AUC_{0-tau} (h*ng/mL)	1328.772 (516.8052)	1054.646 (380.1256)	570.133	1679.877
	$t_{1/2}$ (h)	4.2606 (0.59531)[a]	4.4388 (1.61443)	4.7530	5.9231
	CL_{ss}/F (L/h)	8.261 (2.4193)	11. 039 (5.6978)	17.540	5.953
	Vz_{ss}/F (L)	48.032 (19.3964) [a]	60.637 (6.4561)	120.271	50.869
	AR for C_{max}	1.121 (0.6575)	0.940 (0.3008)	0.679	1.114
	AR for AUC_{0-t}	0.957 (0.2581)	1.014 (0.2754)	0.700	1.124

Abbreviations: AR = accumulation ratio; AUC = area under the concentration-time curve; AUC_{0-inf} = AUC from time 0 to infinity; AUC_{0-24} = AUC from time 0 to 24 hours postdose; AUC_{0-t} = AUC from time 0 to the time of last measurable concentration; AUC_{0-tau} = AUC over a dosing interval (24 hours for QD); CL/F = apparent clearance; CL_{ss}/F = apparent clearance at steady state; C_{max} = maximum observed plasma concentration; $C_{max\ ss}$ = maximum observed plasma concentration at steady state; CP = Child-Pugh; HI = hepatic impairment; N = number of subjects included in the analysis; PHT = portal hypertension;; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to reach C_{max} at; $T_{max\ ss}$ = time to reach C_{max} at steady state;V_z/F = volume of distribution at terminal phase; V_{ss}/F = volume of distribution at terminal phase at steady state.
Note: T_{max} and $T_{max\ ss}$ are presented as median (minimum, maximum) for the 10 mg dose.
CP-A: Mild HI; CP-B: Moderate HI.
All PK parameters for 5 mg are presented as individual values.
[a] n = 4

Pharmacokinetic interaction studies

Table 16: Cut-offs for the evaluation of interaction potential

	50×Cmax(u)[a] (µM)	25×Inlet Cmax(u)[a] (µM)	0.1×dose/250 ml[b] (µM)
Parent drug	0.17	0.75	9
Metabolite M1[c]	0.036	NA	NA
Metabolite M2	0.284	NA	NA
Metabolite M3[c]	0.051	NA	NA

a Multiple dose Cmax, 10 mg daily dose (study CB8025-21629), fu 1%
b Based on a 10 mg dose
c M1 and M3 are not major metabolites
NA - Not applicable

Table 17: Summary of clinical DDI studies

Comparison	Substance Ratio, as Percent (90% CI)		Dosing Recommendation
	C_{max}	AUC_{inf}	
Victim			
Effect of co-administration with fluconazole **CYP2C9 inhibitor**	141 (129, 154)	240 (227, 254)	No adjustment but should be "closely monitored for adverse effects"
Effect of co-administration with carbamazepine **CYP3A4/PXR inducer**	76 (67, 86)	56 (52, 61)	No adjustment
Effect of co-administration with probenecid **OAT1, OAT3, OATP1B1 inhibitor**	469 (426, 516)	200 (182, 219)	Avoid concomitant administration of seladelpar with OAT3 transporter inhibitors
Effect of co-administration with quinidine **P-gp inhibitor**	105 (91, 122)	106 (102, 111)	No adjustment
Effect of co-administration with cyclosporine **BCRP, OATP1B1, OATP1B3 inhibitor**	288 (261, 316)	209 (196, 223)	No adjustment but should be "closely monitored for adverse effects"
Perpetrator			
Effect on midazolam **CYP3A4 substrate**	94 (84, 106)	98 (91, 106)	No adjustment
Effect on tolbutamide **CYP29 substrate**	103 (97-110)	100 (98, 103)	No adjustment
Effect on simvastatin **CYP3A4, BCRP,**	95 (78, 114)	117 (97, 141)	No adjustment

OATP1B1, OATP1B3 substrate			
Effect on rosuvastatin **BCRP, OATP1B1, OATP1B3 substrate**	117 (93, 145)	115 (93, 143)	No adjustment
Effect on atorvastatin **CYP3A4, OATP1B1, OATP1B3 substrate**	127 (89, 195)	113 (76, 168)	No adjustment

*New calculations requested from the applicant

Seladelpar as victim of drug-drug interactions in vivo

The relevance of the positive *in vitro* signals was further investigated in a dedicated clinical study. Five arms in study CB8025-11840 investigated seladelpar as a victim and was designed to assess the effect of fluconazole (CYP2C9 inhibitor), carbamazepine (CYP3A4 inducer), probenecid (OAT3 inhibitor), quinidine (P-gp inhibitor), cyclosporine (BCRP, OATP1B1, OATP1B3 inhibitor), on the PK of seladelpar in healthy subjects under fasting conditions.

Arm A, fluconazole (CYP2C9 inhibitor): At Day 1, 10 mg seladelpar was administered alone and at Day 4 in combination with a single dose of 400 mg fluconazole. As a victim drug, co-administration of seladelpar with fluconazole resulted in an approximately 2.4-fold increase in $AUC_{0\text{-}inf}$ and 41% increase in the C_{max}.

Arm B, carbamazepine (CYP3A4/PXR inducer). The purpose of Arm B was to evaluate the effect of repeated oral doses of carbamazepine, a CYP3A4/PXR inducer on the PK of seladelpar. Carbamazepine was administered in escalating doses from 100 mg BID (Day 4-6) to 200 mg BID (Day 7-10) and 300 mg BID (Day 11-18). Seladelpar was administered at 10 mg on Days 1 and 17. The exposure markedly decreased after co-administration, AUC was reduced by 44% and C_{max} by 24%.

Arm C, probenecid (OAT3, OATP1B1 inhibitor). The purpose of Arm C was to investigate the effect of probenecid on the PK of seladelpar. Seladelpar 10 mg capsules were administered on Day 1 and Day 5, probenecid was administered at 500 mg four times a day from Day 4 to Day 7. Probenecid is an inhibitor of OAT1 and OAT3 as well as an inhibitor of OATP1B1. A clear increase in exposure of seladelpar was seen when co-administrated with probenecid and resulted in a 2-fold increase of AUC and 4.7 increase in C_{max}.

Arm D, quinidine P-gp-inhibitor. The purpose of Arm D was to investigate the effect of quinidine (P-gp-inhibitor) on the PK of seladelpar. On Day 1, a single dose of 10 mg seladelpar was administered alone and on Day 4 in combination with a single dose of 600 mg quinidine. Co-administration with quinidine did not affect the exposure of seladelpar and the ratio of seladelpar vs. quinidine was within in the 90% CI for bioequivalence.

Arm E, cyclosporine (BCRP, OATP1B1, OATP1B3 inhibitor). On Day 1, a single dose of 10 mg seladelpar was administered alone and on Day 4 in combination with a single dose of 600 mg cyclosporine. There was a clear increase in exposure of seladelpar 2.2-fold and 2.9-fold for AUC and C_{max}, respectively.

Seladelpar as a victim of increased gastric pH

There has been no dedicated clinical study to evaluate the effect of acid-reducing agents on the PK of seladelpar. The solubility of seladelpar is pH dependent, being slightly soluble at pH 2 and freely soluble at pH ≥ 6. The proposed therapeutic dose of 10 mg will be fully soluble between pH 6.0 and 6.8, allowing absorption in the small intestine.

Seladelpar as perpetrator of drug-drug interactions in vivo

Seladelpar was investigated as a perpetrator in five *in vivo* studies using midazolam (CYP3A4 substrate), tolbutamide (CYP29 substrate), simvastatin (CYP3A4, BCRP and OATP1B1/OATP1B3 substrate), rosuvastatin (BCRP and OATP1B1/OATP1B3 substrate) and atorvastatin (CYP3A4 substrate).

In study NAP-1002, seladelpar was investigated as a potential inducer of CYP3A4 enzyme. Midazolam was used as probe substrate for CYP3A4. Midazolam was administered (15 mg) to 16 healthy volunteers without seladelpar (Day 1) and after multiple dosing of seladelpar (Days 3 to 16) 200 mg QD. The Statistical analysis comparing C_{max}, AUC_{0-24h} and AUC_{∞} of midazolam and its primary metabolite via CYP3A4 oxidation (1-OH midazolam) alone or co-administered with seladelpar showed a ratio and (90% CI) within in the conventional limits for bioequivalence. Thus, the exposure of midazolam and 1-OH midazolam were not affected by co-treatment of seladelpar.

Study NAP-1004, investigated whether seladelpar inhibits CYP2C9 using tolbutamide as a substrate. It was a three-way, randomised, cross-over, single dose study evaluation the drug-drug interaction of seladelpar (200 mg) and tolbutamide (500 mg) in 15 healthy volunteers. Poor metabolisers of CYP2C9 were excluded from the study. Seladelpar did not affect the pharmacokinetics of tolbutamide or vice versa. Thus, no clinical action is proposed for when seladelpar is co-administered with CYP2C9 substrates.

In study NAP-1003, the interaction potential of simvastatin and seladelpar was investigated. This was a single dose, two-way cross over study conducted in 12 healthy male volunteers. Simvastatin (80 mg) was administered alone or together with seladelpar (200 mg) on Day 1 or 5 depending on randomisation schedule. Simvastatin plasma levels were slightly increased after co-administration with seladelpar but the ratios for AUC and C_{max} were within the conventional limits (90% CI) of bioequivalence. For simvastatins metabolite, simvastatin acid, plasma levels were increased to a higher extent for both C_{max} (2.5-fold) and AUC_{0-12} (1.5-fold) but less for $AUC_{0-\infty}$ (1.2-fold).

Additionally, when the applicant compared seladelpar plasma concentrations to those in a previous study with the same 200 mg dose, the increase in exposure was on average 1.6-fold. When comparing the data there was only a difference in exposure (C_{max} and AUC) and not markedly in elimination. The potential mechanism behind this is unclear.

In study CB8025-11840, the purpose was to evaluate the effect of a single dose seladelpar on the PK of rosuvastatin, a BCRP substrate. On Day 1 a single dose of 20 mg rosuvastatin was administered alone and on Day 8 in combination with a single dose of 10 mg seladelpar. The exposure of rosuvastatin was similar alone or co-administered with seladelpar. No clinical action is suggested by the applicant.

In study MB8025-20711 the pharmacokinetics of seladelpar and atorvastatin was investigated following oral dosing of seladelpar and atorvastatin alone or in combination. There was no clinically meaningful impact on either atorvastatin or seladelpar when co-administered and no clinical action was suggested.

Pharmacokinetics using human biomaterials

<u>Seladelpar as Substrate of Transporters</u>

When tested across a broad range of concentrations up to 450 µM, seladelpar was shown to be a substrate of BCRP and P-gp in MDCKII cells and of OAT3 in HEK293 cells (Study 17081092CBAY). Seladelpar was not a substrate of BSEP.

Seladelpar (up to 15 µM) was not a substrate of MRP2, MRP4, ASBT, NTCP, transporters (Study 17081093CBAY). The accumulation of the metabolites was reduced by specific inhibitors of each transporter.

In study AD-705-2003 it was investigated whether seladelpar is a substrate for human OATP1B1 and OATP1B3 transporters at concentrations of 0.01, 0.03, 0.1, and 0.3 µM. It was concluded that seladelpar is a substrate for OATP1B1 and OAPT1B3 at concentrations up to 0.1 µM. The OATP-mediated uptake was likely saturated at concentrations > 0.3 µM.

Seladelpar as perpetrator of drug-drug interactions in vitro

Table 18: Summary of seladelpar and M2 as an inhibitor of CYP enzymes (pooled human liver microsomes)

Enzyme	Direct inhibition Seladelpar	Direct inhibition M2[b]	Direct inhibition Seladelpar	Direct inhibition M2[c]	TDI	Positive signal to evaluate further
	Ki* (µM)	Ki* (µM)	Ki* (µM)	Ki* (µM)		Yes/No
CYP1A2	>100	>100	>25.0	>25.0	No	No
CYP2B6	NA	NA	>25.0	>25.0	No	No
CYP2C8	NA	NA	6.35	>25.0	No	No
CYP2C9	9.5	26	>25.0	>25.0	No	No
CYP2C19	45	>100	>25.0	>25.0	No	No
CYP2D6	>100	>100	>25.0	>25.0	No	No
CYP3A4	>100	>100	>25.0	>25.0	No	No
CYP3A4	>100	>100	>25.0	>25.0	No	No

*assuming Ki=IC_{50}/2 (only IC_{50} reported by applicant). [a]) Study FK488, TDI not studied, [b]) Study FK5508, TDI not studied, [c]) Study 2402-004-CYP0986_R32. (NA) enzyme not studied.

Table 19: Summary of in vitro enzyme induction of seladelpar, Study CYP09686_R32

	Fold induction mRNA								
	CYP1A2			CYP2B6			CYP3A4		
	Lot A	Lot B	Lot C	Lot A	Lot B	Lot C	Lot A	Lot B	Lot C
0.16 µM	0.884	1.17	1.21	0.663	1.07	1.38	0.662	1.02	1.58
0.4 µM	0.870	1.32	1.22	0.605	1.06	1.28	0.539	1.13	1.34
1.6 µM	0.750	1.05	1.01	0.610	0.965	1.24	0.606	1.14	1.78
4 µM	0.683	0.980	0.904	0.717	0.993	1.18	1.07	1.20	2.21
16 µM	0.496	0.818	0.956	0.865	1.09	1.30	3.12	4.14	7.08
40 µM	0.305	0.629	1.02	0.997	0.958	1.02	2.87	9.91	6.65
Positive control	19.0	28.6	63.1	7.81	12.3	4.07	17.8	81.2	14.0

	Fold induction mRNA								
	CYP2C8			CYP2C9			CYP2C19		
	Lot A	Lot B	Lot C	Lot A	Lot B	Lot C	Lot A	Lot B	Lot C
0.16 µM	1.30	1.43	2.09	0.676	1.12	1.11	0.803	0.932	0.930
0.4 µM	1.28	1.50	1.96	0.631	1.37	1.08	0.763	0.873	0.874
1.6 µM	1.10	1.50	2.00	0.542	1.15	0.999	0.723	0.864	0.934

4 µM	1.23	1.59	2.02	0.545	0.845	0.963	0.716	0.834	0.956
16 µM	1.50	1.86	2.81	0.640	0.853	1.23	0.785	0.926	1.01
40 µM	2.10	1.87	2.95	0.691	0.983	1.20	0.898	0.914	1.18
Positive control	4.54	6.04	2.92	1.58	1.55	2.31	1.35	2.97	1.05

*Positive controls included omeprazole (50 µM) for CYP1A2, phenobarbital (500 µM) for CYP2B6 and rifampicin for CYP2C8/2C9/2C19/3A4 (10 µM)

Table 20: In vitro transporter inhibition

Transporter	Substrate	*In vitro* system	IC_{50} (µM)	Positive signal (Y/N)
P-gp	digoxin; NMQ	MDCKII monolayer inhibition assay and vesicular transporter inhibition assay	156.8	N
BCRP	prazosin; E3S	MDCKII monolayer inhibition assay and vesicular transporter inhibition assay	34.16; 4.32	N Y
OATP1B1	E217βG	Transporter expressing cells	9.585	N
OATP1B3	CCK-8	Transporter expressing cells	2.084	N
OAT1	tenofovir	Transporter expressing cells	-	N
OAT3	E3S	Transporter expressing cells	-	N
OCT2	metformin	cells expressing transporter	-	N
OCT1	metformin	Transporter expressing cells	-	N
MATE1	metformin	Transporter expressing cells	-	N
MATE2	metformin	Transporter expressing cells	-	N
BSEP	taurocholate	Vesicular transporter inhibition assay	-	N

Metabolism Related to UGT Enzymes

Study 2402-004-CYP0986_R32; Seladelpar (0.05 to 50 µM) was also found to inhibit UGT2B7, UGT1A1, UGT1A3, UGT1A4, and UGT1A9 with IC_{50} values of 15.9, 33.5, 31.6, 27.2, and 27.7 µM, respectively. The metabolite M1 (0.1 to 100 µM) inhibited only UGT1A1 with an IC_{50} value of 59.4 µM. The metabolite M2 (0.1 to 100 µM) inhibited UGT1A1, UGT1A4, UGT1A9, and UGT2B7, with IC_{50} values

of 37.2, 37.8, 55.2, and 56.8 µM, respectively. The metabolite M3 (0.1 to 100 µM) did not exhibit any significant inhibition against any UGT tested.

2.6.2.2. Pharmacodynamics

Mechanism of action

According to the applicant is seladelpar a selective PPARδ agonist 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, according to the applicant approximately 630-fold in humans with no evident activation of PPARγ (Report MBX_8025-INV-001).

PPARδ is a nuclear receptor with effects on metabolic and inflammatory pathways (Vázquez-Carrera 2022). PPARδ agonism reduces bile acid synthesis, alters lipid synthesis and metabolism (Haczeyni 2017), and has anti-inflammatory effects in macrophages (Mukundan 2009), including Kupffer cells (Odegaard 2008). Activation of PPARδ by seladelpar in hepatocytes stimulates FGF21 release and signalling which downregulates CYP7A1 enzyme levels, resulting in decreased bile acid synthesis (Kouno 2022). Nonclinical data have also established that seladelpar inhibits intestinal expression of NPC1L1 (RPT013.00), responsible for absorption of cholesterol and the target of the drug ezetimibe (Pirillo 2016).

Clinical data reflect decreased cholesterol absorption with seladelpar. Decreased cholesterol available as a substrate for bile acid synthesis enhances the effect of seladelpar on CYP7A1 in reducing total bile acid pools. In clinical studies of PBC, seladelpar reduced serum levels of C4 (Hirschfield 2023; Jones 2017; Kremer 2022), a biomarker for hepatocellular bile acid synthesis. According to the applicant, recent evidence has emerged for a role of the pruritogenic cytokine IL-31 (Roh 2021) in cholestatic pruritus (Mu 2021). Activation of the bile acid receptor FXR in hepatocytes was shown to produce IL-31 (Xu 2023). Serum levels of bile acids were subsequently found to correlate with serum IL-31 and pruritus in PBC patients, with a dose-dependent reduction in bile acids, IL-31, and pruritus following seladelpar treatment (Kremer 2023).

Primary and Secondary pharmacology

Selected biomarkers for evaluation for pharmacodynamics were ALP (primary biomarker for efficacy in the clinical studies), C4 and Total Bile Acids, Fibroblast Growth Factor 21, Interleukin-31 and Lipids.

Primary pharmacology

Studies on the selected biomarkers were mainly achieved from the clinical studies in patients with PBC. A summary of the results on the selected biomarkers are provided below:

Alkaline Phosphatase

Change in ALP has been assessed in all seladelpar PBC studies. Across PBC clinical studies, reductions in ALP were observed with seladelpar. Onset of ALP reductions have been demonstrated at Week 2 in study CB8025-21528, Week 1 in study CB8025-21629, and Week 4 (the first timepoint assessed) in phase 3 studies CB8025-32048, CB8025-31735, CB8025-31731, and CB8025-31731-RE. In study CB8025-32048, reductions in ALP levels were observed in the seladelpar arm compared with the placebo arm at each timepoint evaluated in the study.

C4 and Total Bile Acids

Both bile acids and C4 (7-alpha-Hydroxy-4-cholesten-3-one), a key circulating intermediate in the hepatocellular biosynthesis of bile acids, have been measured in seladelpar clinical studies in PBC. In the first PBC study with seladelpar, study CB8025-21528, dose-dependent reductions in serum C4 in

PBC subjects treated with seladelpar were first observed (Median Baseline 2 C4 values were 26.750 ng/mL, 15.200 ng/mL, and 12.750 ng/mL in the placebo, MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively. Median percentage changes from Baseline 2 at the last observation on treatment (regardless of the time point of the last dose) were an increase of 29.46% in the placebo group and decreases of 54.85% and 77.02% in the MBX-08025 50 mg and MBX-8025 200 mg groups, respectively).

After 3 months of treatment in the early terminated phase 3 study CB8025-31735, seladelpar 10 mg led to decrease in C4 by -24.83% in compared to -3.58% for the placebo group.

In phase 3 study CB8025-32048, median total bile acid levels at baseline were similar across treatments (5.4 µmol/L in seladelpar vs 7.1 µmol/L in placebo). At Month 6, the median percent change from baseline in total bile acids was -14.0% in the seladelpar arm relative to 8.7% in the placebo arm. At Month 12, the median percent change from baseline in total bile acids was -32.0% for subjects receiving seladelpar compared with -6.6% in those receiving placebo.

Decreases in C4 were also observed with seladelpar treatment in CB8025-32048. At baseline, median C4 values were similar between treatment arms (14.5 ng/mL for seladelpar vs 13.9 ng/mL for placebo). At Month 6, the median percent change from baseline in C4 levels was -39.9% for subjects receiving seladelpar relative to 19.7% for those receiving placebo. At Month 12, the median percent change from baseline in C4 levels was -41.9% for the seladelpar arm compared with 6.4% for placebo.

Fibroblast Growth Factor 21

In CB8025-32048 study, change in FGF21 was assessed as an exploratory endpoint. Data were summarised for all subjects who were randomised and received at least 1 dose of study drug and had baseline and postbaseline serum FGF21 measurements, as defined for the FGF21 Analysis Set. A total of 176 subjects were included in the FGF21 Analysis Set: 120 in the seladelpar arm and 56 in the placebo arm. Among subjects who contributed a sample, a total of 164 subjects (93.2%) completed study dug (seladelpar 113 [94.2%]; placebo 51 [91.1%]) (Report RPT016.00). Mean baseline FGF21 values were comparable between the seladelpar and placebo arms. Absolute and percent changes from baseline and mean values of serum FGF21 levels over the course of the study were evaluated. In subjects receiving seladelpar, postbaseline increases in FGF21 levels were 86.0%, 87.2%, and 76.2% at Months 3, 6, and 12, respectively, versus changes in the placebo group of 15.7%, 1.1%, and 33.5% at these respective timepoints.

Interleukin-31

In CB8025-32048 study, change in IL-31 was assessed as an exploratory endpoint. Data were summarised for all subjects who were randomised and received at least 1 dose of study drug and had baseline and postbaseline serum IL-31 measurements, as defined for the IL-31 Analysis Set. The IL-31 Analysis Set included 120 subjects in the seladelpar arm and 56 subjects in the placebo arm. Subjects with moderate to severe itch at baseline (pruritus NRS ≥ 4), defined as the MSPN-IL-31 Analysis Set, were also analysed for IL-31 changes. The MSPN-IL-31 Analysis Set comprised 44 subjects in the seladelpar arm and 19 subjects in the placebo arm. The majority of subjects in the IL-31 Analysis Set (93.2%) completed study drug (Report RPT015.00). Mean baseline IL-31 values were comparable between the 2 treatment arms in the IL-31 Analysis Set (seladelpar 5.6 pg/mL vs placebo 6.0 pg/mL). Decreases in IL-31 levels were observed in the seladelpar arm at all timepoints evaluated, with least square mean percent changes at Months 3, 6, and 12 of -43.7%, -46.1%, and -38.5%, respectively, versus changes in the placebo group of 34.8%, 5.5%, and 31.4% at these respective timepoints (nominal p≤0.0005 at all study timepoints). Mean baseline IL-31 values in the MSPN-IL-31 Analysis Set were approximately 2-fold higher compared with those in the IL-31 Analysis Set and were comparable between the 2 treatment arms (seladelpar 10.8 pg/mL vs placebo 13.0 pg/mL)

(RPT015.00). Decreases in IL-31 levels were observed in the seladelpar arm at Months 3, 6, and 12 with a least square mean percent change of -39.5%, -44.9%, and -31.6%, respectively, versus changes in the placebo arm of -0.9%, -7.8%, and 7.9% at these respective timepoints.

Lipids

In the phase 3 study CB8025-32048, seladelpar 10 mg treatment led to greater decreases in total cholesterol, LDL-C, and triglycerides levels compared to placebo throughout the course of the study. Consistent reductions were observed in the early terminated phase 3 study CB8025-31735, where at Month 3, median decreases in triglycerides, total cholesterol and LDL-C with seladelpar 10 mg compared to placebo were 20.0% and 1.90%, 6.10% and 2.50%, and 10.50% and 2.75%, respectively.

The following summarises seladelpar effects observed in phase 3 study CB8025-32048:
• Seladelpar led to greater decreases in total cholesterol levels relative to placebo at month 1 and these effects were maintained throughout the course of the study. At Month 12, the least square mean percent change in total cholesterol was -8.6% for seladelpar and -4.2% for placebo.
• Seladelpar led to greater reductions in LDL-C levels relative to placebo at Month 1 and these effects were maintained throughout the course of the study. The least square mean percent change in LDL-C levels was -12.7% for seladelpar and -3.7% for placebo at Month 12.

• Seladelpar led to greater reductions in triglycerides levels relative to placebo at Month 1 and these effects were maintained throughout the course of the study. At Month 12, the least square mean percent change in triglycerides levels was -16.1% for seladelpar and -1.1% for placebo.

Secondary pharmacology

Thorough QT Study CB8025-11733 *Pharmacodynamic Assessment of Seladelpar on Cardiac Repolarization in a Single Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Seladelpar*

This was a single-centre, randomised, partial-blind, single-period, parallel-group study designed to assess the effect of a single oral dose of 10 or 200 mg seladelpar compared with placebo on ECG parameters in eligible healthy male and female subjects. Moxifloxacin 400 mg served as a positive control and was given without blinding. The study is described in the safety section and does not evoke any concerns.

Relationship between plasma concentration and effect and safety

Exposure-response (E-R) analyses for efficacy and safety were conducted in a pooled population that included PBC patients from the Phase 2 study CB8025-21629 and Phase 3 studies CB8025-32048, CB8025-31735, CB8025-31731, and CB8025-31731-RE. In total, 63% of the subjects included in the analysis had no PK measurements; their exposures were predicted based on population parameter estimates and the subjects' covariate data. Most patients received the 10 mg dose, and although some patients started on a lower dose, dose titration was allowed after a certain number of weeks, confounding the analyses. Due to the limited nature of the data, these analyses are not further described.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalysis

The pivotal bioanalytical method is MN15102 described in validation report MC15B-0190 which is used for analysis of seladelpar in later studies with doses in therapeutic dose range.

No cross-validation was performed between validation MC15B-190 and validation BA428 used in bioanalysis of early phase studies (Studies NAP-1001, NAP-1002, NAP-1003, NAP-1004, NAP-1005). This is considered acceptable since different dose-levels are used, with higher doses in the early studies and doses in therapeutic dose range in the later studies.

The bioanalytical reports for studies NAP-1001, NAP-1002, NAP-1003, NAP-1004, NAP-1005 are missing. According to the applicant these bioanalytical reports were generated by Johnson & Johnson Pharmaceutical Research & Development and are not available for this submission. This is considered acceptable since the studies are early studies with higher doses. Absence of these bioanalytical reports is also considered acceptable for the DDI-part of the studies, since seladelpar is evaluated as a perpetrator in studies NAP-1002, NAP-1003 and NAP-1004.

The applicant reassures, that all PK data presented in this submission are derived using bioanalytical methods with extraction on ice, hence interconversion during sample preparation should be at a minimum not interfering with the performance of the procedures.

Population PK

Two popPK analyses were conducted, one for seladelpar and one for the M2 metabolite. Since the clinical activity of M2 is insignificant, only the popPK analysis of seladelpar is reported and assessed.

Due to a poor model fit to patient data, the applicant was requested to redo the population PK analysis and fit the new model to only patient data. The applicant has provided an updated analysis; however, the model was still fitted to pooled data from both healthy subjects and patients. Overall, the modelling strategy in the updated analysis is acceptable, although it is questionable if the data from healthy subjects adds anything to the description of PK in PBC patients. There are several covariate effects included to account for differences between healthy subjects and PBC patients, and despite this, the model is still underpredicting clearance in PBC patients. The updated model is, however, providing a better description of PBC patient data than the original model. Furthermore, the applicant has conducted a sensitivity analysis in which the final model was fitted to only PBC patient data. Parameter estimates were overall similar between the sensitivity analysis and the final model analysis. The only parameters with a more pronounced difference in estimates between the model fits were the apparent peripheral volume of distribution (51 L in the sensitivity analysis versus 26 L in the final model analysis), and absorption related parameters (zero-order release duration and first-order absorption rate; this difference was expected given the known difference in absorption rate between fasted and fed subjects in combination with the foodwise uncontrolled patient data). It would have been interesting to compare pcVPCs for the sensitivity analysis with the provided pcVPCs for the final model analysis, to see how much better the model fits the PBC patient data when it is fitted to only these data. However, given the relative similarity between the two model fits, no clinically relevant conclusions are expected to change, and the issue is therefore not further pursued.

PBPK

Two PBPK analyses were conducted, one to evaluate clinically relevant dissolution specifications and assess DDIs with CYP enzymes, and one to assess DDIs with different transporters. Since no claims

are based on the PBPK analysis on DDIs with transporters, this analysis is neither reported nor assessed.

The IVIVE-based absorption model was only validated against data from the final capsule formulation and data from DSIC, while the IVIVC-based absorption model was only validated against data from the final capsule formulation (clinical study CB8025-11836). This is considered insufficient, and although the clinical data suggests that drug absorption is insensitive to differences in the drug formulation, the PBPK model is not qualified to support any dissolution specifications.

The elimination part of the PBPK model was only validated against data from clinical study CB8025-11840, where seladelpar was administered concomitantly with fluconazole and carbamazepine, respectively. Fluconazole is a moderate inhibitor of CYP2C9 and CYP3A4, and carbamazepine is an inducer of CYP3A4, but also inducer of other CYP enzymes such as CYP2C8 and CYP2C9. The metabolism of seladelpar is complex and it is not sufficient to only validate the PBPK model against data from a two-part drug-drug interaction study. Furthermore, both fluconazole and carbamazepine are affecting more than one of the enzymes involved in the metabolism of seladelpar and it is hence neither possible to verify, nor to dismiss, the relative contribution of respective enzyme using these data.

The PBPK model is not sufficiently qualified, but no claims were based this model.

ADME

Absorption of seladelpar is sufficiently characterised in several clinical studies with different formulations, with and without food.

The results of *in vitro* permeability data are not considered conclusive, and no absolute bioavailability study was conducted. However, the results from the oral mass balance study indicate that seladelpar is a compound with a high fraction absorbed, >85%, and hence a highly permeable compound.

Two relative bioavailability studies were submitted: study NAP-1005 comparing Solution and Formulation 1, and study CB8025-11836 comparing DSIC and Formulation 2 (to-be-marketed solution). No comparison has been performed between the two early formulations (solution and Formulation 1) and the two capsule formulations (DSIC and Formulation 2). However, no relative bioavailability study between early formulations (oral solution/Formulation 1) and capsule formulations (DSIC/Formulation 2) was requested. Indeed, the results would probably be difficult to interpret due to that different dose levels used for the two pairs of formulations, with higher doses (≥50 mg) with the early formulations (oral solution/Formulation 1) and lower doses (≤25 mg) with the capsule formulations (DSIC/Formulation 2) and in addition the plasma exposure increase slightly more than proportional to dose at higher doses. It needs to be taken into account when comparing results from studies where an early formulation has been administered with results from studies where DSIC or to-be-marketed capsule formulation has been administered. For example, when evaluating the polymorphism of CYP2C9, results are compared between individuals administered with solution formulation and individuals administered with the to-be-marketed formulation.

The food interaction studies showed similar AUC of seladelpar and somewhat lower C_{max} (32%) and delayed t_{max} by approximately 2.5 hours in fed conditions compared to fasted conditions. In the Phase 3 clinical studies there was no specific requirement to take seladelpar with or without food. There was however a recommendation that individuals should be fasted prior to PK blood sampling. The efficacy and safety results were then evaluated in subjects independently of food intake, and intake with or without food is therefore acceptable.

Predictions of inter-individual variability in exposure based on the updated population PK analysis show moderate inter-individual variability in seladelpar exposure following oral administration of Seladelpar Gilead.

The study design of the mass balance study with single dosing of ^{14}C-seladelpar is adequate since there are no major dose- or time-dependencies in the first pass metabolism or elimination of the drug. Sufficient recovery was obtained in the mass balance study (92.9%). The ^{14}C-labelling is in a stable position and acceptable.

Seladelpar was extensively metabolised following an oral dose of ^{14}C-seladelpar with 13 identified and characterised metabolites and additional five quantified, but not structurally characterised metabolites in plasma, urine and faeces.

There is one major metabolite in plasma, M2, which accounted for 17.6% of the total plasma radioactivity. Seladelpar accounted for 8.1% of the total plasma radioactivity in the same study. Hence, metabolite M2 has an AUC both larger than one fourth of the AUC of parent drug and larger than 10% of the drug-related exposure (radioactive moieties in the mass-balance study) and is defined as a major metabolite according to the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**). The metabolite M2 has some PPARδ activity but low compared to seladelpar (approximately 131-175 times lower). The metabolite M2 is not estimated to contribute to efficacy *in vivo*, considering similar protein binding and an approximately double plasma exposure.

Seladelpar drug substance has one stereogenic centre and is being developed as a single enantiomer of the R-configuration. A second stereocentre is introduced by relatively enantio-nonspecific sulfoxidation for the M1 and M3 metabolites and the original chiral centre of seladelpar has not converted. The chiral inversion of seladelpar is highly unlikely since there is no chemically plausible mechanism for the chiral inversion of the ethyl-ether stereocentre and therefore a chiral analysis method for seladelpar is not needed.

As CYP2C9 is considered the major metabolic pathway of seladelpar and this enzyme is polymorphic, the applicant has evaluated if individual genotypes of CYP2C9 affect the PK of seladelpar. A reanalysis was performed including the 8 subjects that previously have been defined as indeterminate. There is a risk of increased plasma exposure of seladelpar in poor metabolisers of CYP2C9, but an exact figure of the maximum increase could not be calculated. The present results showed similar Cmax and 18% increase in AUC∞ when comparing intermediate metaboliser versus normal metaboliser but no conclusion could be made for poor metabolisers due to too few individuals. The plasma exposure in the one identified poor metaboliser in study 11840 was approximately doubled compared to mean AUC/dose in normal metabolisers. This subject was assigned the CYP2C9 phenotype *3/*2. It should be noted that the effect is larger in subjects who are CYP2C9 poor metabolisers with *3/*3 compared to subjects with *3/*2.

The present results are showing a risk for increased plasma exposure in patients that are CYP2C9 poor metabolisers. The results of increase in plasma exposure in poor metabolisers was not included in the SmPC section 5.2 due to that there was only one subject identified as poor metaboliser. The maximum increase in plasma exposure could not be estimated due to the few individuals identified as poor metabolisers. There is no recommendation of genotyping of patients. This is considered acceptable since the patients are monitored with regular laboratory evaluation of liver tests (SmPC section 4.4) although transaminase elevations were seen in earlier studies with higher doses of seladelpar (50 mg and 200 mg).

The metabolism in a CYP2C9 poor metaboliser is also unknown regarding which enzymes are main metabolizing enzymes, the extent of metabolism and which metabolites are formed. There could hence be a risk of increased plasma exposure of seladelpar in individuals that are poor metabolisers when

they are concomitantly administered with a compound that is an inhibitor of the metabolizing enzyme. This risk is difficult to evaluate but monitoring of liver tests as described in SmPC section 4.4 is considered sufficient to detect individuals with increased plasma exposure.

According to the applicant, genotyping for CYP2C9 in the ongoing hepatic impairment study (21838) will be performed after study completion. It is acknowledged that, in this study, correlation of CYP2C9 genotyping to exposure may be confounded by different levels of hepatic impairment. Nevertheless, in light of the missing information on which CYP´s, apart from CYP2C9, is/are responsible for metabolising seladelpar, this information is considered important, as it could shed light on the impact of CYP2C9 being polymorphic. Hence, this study should be submitted as soon as possible, but submission is acceptable as a post approval measure (recommendation). The applicant is recommended to submit the study as soon as final study results are available. The study is currently ongoing, and the final study report as well as the pharmacogenomic analysis on cytochrome P450 (CYP)2C9 from this study is anticipated to be available by June 2025.

Therapeutic window

The applicant has defined the upper bound of the no-effect boundary as 2-fold of median steady state seladelpar exposure (C_{max} and AUC) following 10 mg once daily doses of seladelpar in PBC subjects. The rationale presented for the upper bound of the no-effect boundary is considered acceptable.

The applicant has defined the lower bound of the no-effect boundary as 2-fold lower than the median exposure (C_{max} and AUC) of seladelpar following 10 mg once daily doses of seladelpar in subjects with PBC. The rationale put forward by the applicant for the lower bound of the no-effect boundary is acceptable. However, some drugs i.e. CYP2C9/CYP3A4-inducers, seems to decrease AUC with 44 % which could be important to inform the prescribers about. Information regarding CYP3A/CYP2C9 inducers, with specific mentioning of rifampicin, with information to the prescribers that these drugs may decrease the efficacy have been included in section 4.5.

Special populations

The majority (>70%) of seladelpar related radioactivity was excreted as metabolites in urine in the AME study. Seladelpar was not detected in urine.
The applicant presented a new evaluation of the impact of renal impairment on the exposure to seladelpar (total and fraction unbound) after reclassification of subjects according to guideline (absolute GFR).

Referring to the defined no-effect boundaries, a 2-fold increase in seladelpar exposure is considered safe. When evaluating total seladelpar, a less than 2-fold increase is observed in all the three groups of subjects with renal impairment. Whereas for the unbound values some endpoints result is slightly more than 2-fold increase in exposure between normal matched and renally impaired subjects. The inherent variability of determining fraction unbound for compounds of >99% binding is acknowledged. Hence for seladelpar, it is agreed that renal impairment would have limited impact on the safety of seladelpar.

A hepatic impairment study was performed in PBC patients, and an increase in plasma exposure of seladelpar of 1.6-1.9-fold was seen in Cohort 2 (PBC patients with Child-Pugh A and PHT) and Cohort 3 (PBC patients with Child-Pugh B, moderate HI) compared to Cohort 1 (PBC patients with Child-Pugh A, mild HI). The study is ongoing in Cohort 4 (PBC patients with Child-Pugh C, severe HI). The plasma protein binding was similar as previously reported *in vitro* protein binding of >99.5 - 99.7% (fu <0.5% - 0.3%) and using total plasma PK parameters in the evaluation of this study is considered acceptable.

Genotyping for CYP2C9 in the ongoing hepatic impairment study will be performed after study completion. The applicant is asked to commit to submit the final study report as a post approval measure, see (recommendation) above.

There was an indication of gender differences in the plasma PK results in the mass balance study. The data was limited with only 4 males and 4 females and not conclusive, however a 1.6-fold higher plasma exposure in females could be acceptable considering the therapeutic window of seladelpar. No special labelling guidance with respect to dosage and administration is needed for gender.

In the population PK analysis, neither race nor ethnicity were identified as covariates. The table including number of elderly subjects in pharmacokinetic studies have been submitted.

Interactions

Seladelpar as victim of drug-drug interactions in vitro

None of the metabolites M1, M2 or M3 are considered as pharmacologically active and are therefore not assessed from a victim perspective.

The results of *in vitro* phenotyping studies showed that M1 was formed primarily by 2C8 with additional contributions in the order of 3A4>2C9. M2 was generated predominantly by 2C9 with minor formation by 2C8. M3 was produced predominantly by 2C9 with minor contribution from 2C8, 3A4 and possibly 2C19. The relevance of CYP2C9 inhibition and CYP3A4/PXR induction was investigated in dedicated clinical studies.

Seladelpar as victim of drug-drug interactions in vivo

The relevance of the positive *in vitro* signals was further investigated in a dedicated clinical study. Five arms in study CB8025-11840 investigated seladelpar as a victim and was designed to assess the effect of fluconazole (CYP2C9 inhibitor), carbamazepine (CYP3A4/PXR inducer), probenecid (OAT3, OATP1B1 inhibitor), quinidine (P-gp inhibitor), cyclosporine (BCRP, OATP1B1, OATP1B3 inhibitor), on the PK of seladelpar in healthy subjects under fasting conditions.

The effect of a CYP2C9 inhibitor on the PK of seladelpar was investigated using fluconazole. At Day 1, 10 mg seladelpar was administered alone and at Day 4 in combination with a single dose of 400 mg fluconazole. The selected fluconazole dose of 400 mg appears acceptable for the study purpose, but the study design does not reflect worst case scenario. Fluconazole is recommended as a CYP2C9 inhibitor in the EMA DDI guideline. But it should be noted that it is only a moderate CYP2C9 inhibitor (as well as a moderate CYP3A inhibitor).

Also, since no strong inhibitors of CYP2C9 are available it is preferable to investigate the effect of pharmacogenetics to quantify enzyme contribution if possible. However, no such data has been presented for this study alone and only one poor metaboliser of CYP2C9 has been included in the overall analysis of CYP2C9 polymorphisms effect on seladelpar PK.

As a victim drug, co-administration of seladelpar with fluconazole resulted in an approximately 2.4-fold increase in $AUC_{0\text{-}inf}$ and 41% increase in C_{max}. This is within the defined therapeutic window and the applicant proposes that when seladelpar is concomitantly administered with medicinal products that are strong CYP2C9 inhibitors, or dual moderate CYP2C9 and moderate to strong CYP3A4 inhibitors (e.g. fluconazole), patients should be closely monitored for adverse effects including monitoring of hepatic laboratory values. This is acceptable.

When seladelpar was co-administered with carbamazepine (PXR/CYP2C9/CYP3A4 inducer) the exposure of seladelpar markedly decreased, AUC was reduced by 44% and C_{max} by 24%. However, no clinical action is recommended for this scenario. Information regarding CYP3A/CYP2C9 inducers, with specific

mentioning of rifampicin, with information to the prescribers that these drugs may decrease the efficacy has been included in section 4.5.

According to *in vitro* studies seladelpar is a substrate of OATP1B1, OATP1B3, BCRP, Pgp, and OAT3 transporters which was further investigated in clinical DDI studies. Quinidine (Pgp-inhibitor) had no effect on the exposure and no clinical action is warranted. For cyclosporin (BCRP-, OATP1B1- and OATP1B3-inhibitor) and probenecid (OAT1-, OAT3- and OATP1B1-inhibitor) a clear increase in exposure was seen and the SmPC 4.5 states that the concomitant administration of seladelpar with probenecid is not recommended which is acceptable. The applicant was also asked to update section 4.5, listing drugs inhibiting OATP1B1, OATP1B3, BCRP and OAT3 that are relevant for this patient population. The applicant included cyclosporin as an example which is acceptable.

Seladelpar as a victim of increased gastric pH

There has been no dedicated clinical study to evaluate the effect of acid-reducing agents on the PK of seladelpar. The solubility of seladelpar is pH dependent, being slightly soluble at lower pH and freely soluble at pH ≥ 6. This usually requires a dedicated PPI study. However, a higher pH and consequently higher solubility in the stomach is not likely to affect the already high fraction absorbed of >85%. In conclusion, no dedicated DDI-study is considered necessary.

Seladelpar as perpetrator of drug-drug interactions in vivo

Seladelpar was investigated as a perpetrator in five *in vivo* studies using midazolam (CYP3A4 substrate), tolbutamide (CYP29 substrate), simvastatin (CYP3A4, BCRP and OATP1B1/OATP1B3 substrate), rosuvastatin (BCRP and OATP1B1/OATP1B3 substrate) and atorvastatin (CYP3A4 and OATP1B1/OATP1B3 substrate). In conclusion, seladelpar did not affect the exposure of the substrate drugs in a clinically relevant way. Thus, no clinical action of seladelpar as a perpetrator is proposed. This is acceptable.

2.6.4. Conclusions on clinical pharmacology

The pharmacology of seladelpar is considered sufficiently characterised for marketing authorisation. The applicant informs that genotyping for CYP2C9 in the ongoing hepatic impairment study (21838) will be performed after study completion and the result of this study is recommended to be submitted as soon as final study results are available which is anticipated by June 2025.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

The dosing regimen proposed for commercial use is 10 mg seladelpar once daily. This is the same dose evaluated in the pivotal study CB8025-32048. The selection of this dose was based on open-label phase 2 clinical data (CB8025-21629), as well as efficacy and safety results of the placebo-controlled phase 3 study (CB8025-31735).

Initially higher doses of seladelpar (50 mg and 200 mg) were studied (CB8025-21528) and led to improvements in markers of cholestasis but also resulted in transaminase elevations and development of these dose levels was abandoned. The high doses were selected since decreases in ALP had been noted at daily doses of 50 mg and 100 mg over 8 weeks in subjects with mixed dyslipidaemia, and 200 mg over 21 days in healthy volunteers. Available clinical data suggested that seladelpar at a daily oral dose of up to 100 mg for up to 8 weeks in males and females and at a daily oral dose of 200 mg

for up to 3 weeks were well tolerated and generally safe. Because these data were obtained in subjects who did not have PBC, it was anticipated that higher dose might be necessary in PBC. However, due to the safety findings of transaminase elevation in study CB8025-21528, lower doses were examined in the following dose ranging study.

Study CB8025-21629

This was a phase 2, open-label, randomised, 52-week dose-ranging (seladelpar 2, 5, 10 mg once daily) study designed to evaluate safety and efficacy in subjects with PBC who had an inadequate response or an intolerance to UDCA. Subjects with an inadequate response to UDCA received seladelpar in addition to standard of care UDCA treatment, while subjects with intolerance to UDCA received seladelpar as monotherapy.

The study was initially designed to include an 8-week dose-ranging period followed by an 18-week extension period. After a Screening Period of up to 2 weeks eligible subjects were randomly assigned 1:1 to seladelpar 5 or 10 mg once daily. Once 24 subjects were enrolled, Interim Analysis 1 was completed to determine whether a 25 mg cohort should be enrolled. On completion of this efficacy and safety analysis the protocol was amended to add a 2 mg once daily cohort (up to 18 subjects) and to increase the dose-ranging period from 8 to 12 weeks, the sample size to 116, and extend the total treatment period to 52 weeks.

Beginning at Week 12 (or Week 26 for subjects with cirrhosis), subjects in the 2 or 5 mg groups could have their dose up-titrated to 10 mg once daily, based on individual review of their ALP response and evaluation of safety and tolerability. After completion of the 52-week treatment period, subjects could elect to roll over into the long-term study, study CB8025-31731. Each subject's safety and efficacy reviews were performed by the Investigator in collaboration with the Medical Monitor and were based on their clinical judgement, considering the safety and tolerability of seladelpar and the biochemical response to seladelpar (e.g., achieving a meaningful decrease in ALP). Dose down-titration was performed for safety reasons and was allowed at any time during the study. A total of 119 subjects received treatment, including 15 subjects who had participated in a prior seladelpar study (study CB8025-21528). Subjects initially received seladelpar 2 mg (n = 11), seladelpar 5 mg (n = 53), and seladelpar 10 mg (n = 55). Most subjects (105 subjects, 88.2%) completed 52 weeks of treatment with seladelpar. Thirteen of 14 subjects whose treatment was discontinued early received seladelpar 5 or 10 mg (7 and 6 subjects, respectively). The most common reason for early discontinuation of treatment was withdrawal of informed consent (n = 6 subjects). Four subjects discontinued treatment early because of AEs, including 3 subjects who received seladelpar 5 mg (up-titrated to 10 mg in 1 subject), and 1 who received seladelpar 10 mg; 1 of these subjects (seladelpar 5-mg group) met liver safety monitoring criteria.

The primary efficacy endpoint was mean percent change in ALP from baseline to Week 8 of treatment. Secondary efficacy endpoints included absolute and mean percent change in ALP from baseline to 12 and 52 weeks of treatment; composite endpoint of ALP and total bilirubin (ALP < 1.67× ULN, ≥ 15% decrease from baseline in ALP, and total bilirubin ≤ ULN); and change and percent change from baseline in designated biochemistry parameters (total bilirubin, GGT, AST, ALT).

Results:

The primary efficacy endpoint of mean (95% confidence intervals [CIs]) 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 different from the change in the 2 mg dose group (p = 0.0021) and the 5 mg dose group (p = 0.0024). After 12 weeks of dosing, mean (95% CI) percent changes from baseline in ALP were -

22.6% (-31.9%, -13.2%), -34.5% (-40.5%, - 28.4%), and -43.2% (-46.7%, -39.7%) for the 2, 5, and 10 mg dose groups.

ALP normalisation rates at 12 weeks were 0%, 10.6%, and 31.4% for the 2, 5 and 10 mg dose groups, respectively. By Week 52, 10 subjects in 2 mg dose group were up-titrated to 5 or 10 mg; 30 subjects in the 5 mg treatment group were up- titrated to 10 mg; and 14 subjects with an initial dose of 5 mg stayed on the 5 mg dose.

A total of 11 subjects in the 5 and 10 mg dose groups met the safety monitoring criteria: 4 subjects for liver (ALT, AST, or bilirubin), 4 subjects for muscle (creatine kinase), and 4 subjects for pancreas (amylase or lipase). All subjects with creatine kinase elevation had clear clinical explanations and/or creatine kinase returned to within normal limits while on study drug when retested. Subjects who met safety monitoring criteria for pancreas had transient increase in amylase or lipase or were considered as not clinically significant. None of the subjects on study met the safety monitoring criteria for serum creatinine.

Study CB8025-31735 (ENHANCE)

Study CB8025-31735 was a phase 3 study with a double-blind, randomised, placebo-controlled 52-week dose-ranging (placebo, seladelpar 5 mg once daily [with blinded titration of non-responders to 10 mg once daily at Month 6], seladelpar 10 mg once daily) parallel treatment group design. This study was planned to be a pivotal study to evaluate the safety of seladelpar and its effect on biochemical and other markers of cholestasis and on pruritus in subjects with PBC who had an inadequate response or intolerance to UDCA. For subjects who tolerated UDCA, seladelpar was administered as an add-on to standard of care UDCA therapy. For subjects with an intolerance to UDCA, seladelpar was administered as monotherapy.

The study was terminated early due to EOT histology findings in a concurrent phase 2 study of seladelpar in subjects with NASH. On 25 November 2019, as a precautionary measure until the NASH study histology findings could be understood, the study was put on hold and subjects stopped treatment with study drug. On 20 December 2019, the study was terminated.

A Screening Period of up to 2 weeks was followed by dispensing of e-diaries at the beginning of a 2-week Run-in Period. E-diary questionnaires included the Pruritus NRS, 5-D Itch Scale, PGI-S, PGI-C, and PBC-40 QoL.

Subjects performed a daily evaluation of their pruritus using the Pruritus NRS beginning at the Run-in Visit through the first 26 weeks (6 months) of treatment. After 26 weeks, Pruritus NRS was evaluated daily for 7 consecutive days each month. The 5-D Itch Scale was evaluated biweekly from the Run-in Visit up until the Month 6 visit and, then each clinic visit until the Month 12 visit. The PBC-40 and PGI-S were evaluated at each clinic visit over the entire study duration. PGI-C was collected at each clinic visit starting from Month 1.

At the conclusion of the Run-in Period, subjects were randomly assigned 1:1:1 to study drug (placebo:seladelpar 5 mg:seladelpar 10 mg). Randomisation was stratified by screening ALP level (< 350 vs ≥ 350 U/L) and pruritus status (Pruritus NRS < 4 vs ≥ 4). Eligible subjects entered a treatment period of up to 52 weeks.

For all subjects completing the first 6 months of treatment with blinded study drug (placebo or seladelpar), a blinded evaluation of the initially assigned dose was performed. Subjects assigned to the seladelpar 5/10 mg arm who were not responders based on the composite response rate at Month 6 and were tolerating study drug were up-titrated from seladelpar 5 to 10 mg for the remainder of the study. Subjects initially assigned to placebo or seladelpar 10 mg continued on their original treatment

assignment. To avoid unblinding, all subjects attended a dose adjustment visit, which occurred 2 weeks after the Month 6 visit.

Efficacy assessments included markers of cholestasis (ALP, total bilirubin) and pruritus by NRS. Additional assessments included other biochemistry laboratory parameters (including GGT, ALT, and AST), and other pruritus assessments (5-D Itch Scale, PGI-S, PGI-C, PBC-40).

Safety assessments included reporting of AEs, laboratory testing (haematology, biochemistry, serum pregnancy), ECGs, vital sign measurements, and physical examinations. Predefined safety monitoring criteria provided guidance to Investigators on monitoring and study drug interruption or stopping criteria in the event of laboratory clinical findings concerning for potential liver, muscle, renal, or pancreatic injury.

The primary efficacy endpoint was the proportion of subjects achieving the composite biochemical response of ALP < 1.67× ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ ULN with seladelpar compared with placebo at 12 months. Subjects with missing data for any reason were imputed as non-responders.

Key secondary efficacy endpoints were incidence of normalisation of ALP at Month 12 and mean change from baseline in Pruritus NRS at Month 6. Subjects with missing data for the endpoint of normalisation of ALP for any reason were imputed as non-responders.

As a result of the early study termination and the small number of subjects who had reached the 52-week timepoint, the timepoint for the primary and key secondary efficacy endpoints was amended to a 3-month timepoint before the study was unblinded.

Analysis of the primary endpoint was conducted using the same approach used in analysis of the primary endpoint in study CB8025-32048. The first key secondary efficacy endpoint of incidence of normalisation of ALP at Month 3 was analysed similarly to the primary endpoint. Change from baseline in Pruritus NRS at Month 3 was analysed by using an ANCOVA model with term for treatment factor and baseline pruritus score as covariate.

Efficacy endpoints were analysed for the mITT analysis set. The robustness of the primary efficacy analysis was explored using worst-case and tipping point analyses on the mITT analysis set. Sensitivity analyses of the primary analysis were repeated for the ITT and PP analysis sets. The ITT set included any subject randomly assigned to study drug. The PP set included any subject randomly assigned to study drug who received at least 1 dose of study drug, had at least 1 postbaseline ALP and total bilirubin evaluation, and did not have a protocol violation that was deemed to impact the efficacy analysis.

Subject Disposition and Exposure to Study Drug

A total of 501 were screened, and 265 subjects were randomised into the study. All 265 subjects received at least 1 randomised dose: 87 subjects received placebo, 89 subjects received seladelpar 5 mg, and 89 subjects received seladelpar 10 mg. Only 5 subjects in the study were up-titrated from an initial dose of 5 mg to 10 mg, therefore, this population were not presented in the efficacy analyses.

On 25 November 2019, at the time the study was placed on hold, all subjects who were receiving study drug (n = 254) were asked to discontinue dosing as soon as possible and schedule a safety follow-up visit; the study was subsequently terminated on 20 December 2019. Before the 25 November 2019 study hold, 2 subjects had completed treatment, 3 subjects had discontinued for non-safety reasons, and 5 subjects (1.9%) discontinued treatment early due to safety reasons, including 1 subject in the placebo arm who experienced an AE that met liver safety monitoring criteria, and 4 subjects who experienced AEs that did not meet safety monitoring criteria (2 subjects had received seladelpar 10 mg, 1 subject had received seladelpar 5 mg, and 1 subject had received placebo).

At the time of study termination, median duration of exposure to seladelpar was 16.071 weeks (16.571 and 15.571 weeks in the seladelpar 5 and 10 mg, arms, respectively) and ranged from< 1 to 52 weeks. The majority of subjects (105 subjects, 58.9%) had received seladelpar for >12 weeks, with 34.3% (61 of 178 subjects) having received seladelpar for between 12 and 26 weeks. Among subjects in the placebo arm, median duration of exposure was 17.714 weeks and ranged from 2.429 to 47.857 weeks. Similar to those subjects who received seladelpar, most subjects in the placebo arm (54 of 87 subjects, 62.1%) had received treatment for > 12 weeks, with 36.8% (32 of 87 subjects) having received between 12 and 26 weeks of treatment. The maximum treatment duration across all study arms was 52 weeks.

Demographic and Characteristics

Of the 265 subjects enrolled, 250 (94.3%) were female. Subjects ranged in age from 30 to 75 years; their mean age was 55.4 years, with majority of patients being under 65 years old (83.4%). Subjects' mean weight and BMI were 73 .29 kg and 27.81 kg/m 2, respectively. Most of the enrolled subjects (90.6%) were white and mostly enrolled in North America (46.0%) or Europe (40.0%). Demographic characteristics were comparable across analysis sets. For all subjects, the mean duration of PBC was 8.4 years. The majority of subjects was treated with UDCA for 6.8 years. The study enrolled 16 subjects intolerant of UDCA. Enrolled subjects were well-balanced between the groups for levels of biochemical markers of cholestasis inclusive of those used for endpoint analysis. At baseline, mean ALP was 293 U/L, 290 U/L, and 291 U/L in the placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively. Baseline mean total bilirubin was 0.71 mg/dL, 0.76 mg/dL, and 0.72 mg/dL placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively.

The study enrolled 81 subjects (30.6%) with NRS ≥4, and these subjects were also equally divided between treatment groups: 27 subjects (31%) in the placebo group, 27 subjects (30.3%) in the seladelpar 5 mg group, and 27 subjects (30.3%) in the seladelpar 10 mg group, and their mean baseline NRS were 6.08, 6.07 and 6.19, respectively. A mean NRS score for all subjects was 2.80. All subjects had MELD scores of <12 at baseline. The baseline Rotterdam disease score was mild in 233 subjects (87.9%) and moderately advanced in 32 subjects (12.1 %); there were no subjects with advanced disease.
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%)

Efficacy results at Month 3

A total of 56, 56, and 55 subjects in the placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively, were evaluated at Month 3.
The response rate for the primary efficacy composite endpoint of ALP and total bilirubin after 3 months of treatment was 12.5%, 57.1%, and 78.2% in the placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively. These results were statistically significant for both seladelpar groups when compared against placebo (p<0.0001, 95% confidence interval (CI): 65.0, 88.2 for 10 mg group, 95% CI: 43.2, 70.3 for 5 mg group, and 95% CI: 5.2, 24.1 for the placebo group).
The study also met the key secondary endpoint of ALP normalisation. After 3 months of treatment, ALP was normalised in 27.3% of subjects treated with seladelpar 10 mg (95% CI: 16.1, 41.0, p<0.0001), which was higher compared to the placebo (0% [95% CI: 0, 6.4]) and seladelpar 5 mg (5.4% [95% CI: 1.1, 14.9], p=0.0839) groups.
The key secondary endpoint of change in pruritus NRS was also met. Pruritus NRS was ≥4 at baseline

in 27 subjects (31.0%) in the placebo group, 27 subjects (30.3%) in the seladelpar 5 mg group, and 27 subjects (30.3%) in the seladelpar 10 mg group. At baseline, the placebo, seladelpar 5 mg, and seladelpar 10 mg groups reported mean (SD) scores of 6.08 (1.234), 6.07 (1.366), and 6.19 (1.441), respectively. After 3 months of treatment the change from baseline pruritus NRS LS mean (SE) decreased by 1.55 (0.455), 2.01 (0.467), and 3.14 (0.455) in the placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively; with the LS mean difference (95% CI) of -0.46 (-1.77, 0.84) for the seladelpar 5 mg group and -1.59 (-2.87, -0.30) for the seladelpar 10 mg group versus the placebo group. The difference was statistically significant for the seladelpar 10 mg group (p=0.0164) compared to the placebo group.

2.6.5.2. Main study

CB8025-32048 (RESPONSE): A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)

Methods

The primary evidence of the efficacy of seladelpar in the proposed indication is provided by study CB8025-32048 (RESPONSE), a phase 3, double-blind, randomised, placebo-controlled study conducted in subjects with a diagnosis of PBC and an inadequate response or intolerance to UDCA. The study evaluated oral seladelpar 10 mg once daily versus placebo over 12 months (52 weeks).

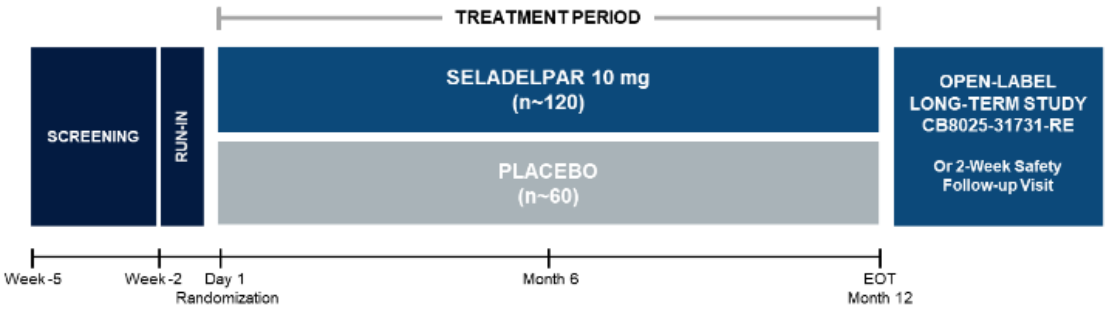
During the Run-in Period, subjects were instructed to begin a pruritus evaluation using an electronic diary (e-diary). On Day 1, subjects were randomly assigned in a 2:1 ratio to receive daily seladelpar 10 mg or placebo. Randomisation was stratified by ALP level (< 350 U/L vs ≥ 350 U/L) and the presence of clinically important pruritus (Pruritus NRS < 4 vs NRS ≥ 4).

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.

After completion of the Treatment Period, subjects were invited to enrol into an open-label, long-term study (CB8025-31731-RE) wherein each subject was to be administered seladelpar, and subjects previously randomised on placebo were to initiate seladelpar treatment. Subjects who discontinued study drug treatment for any reason other than a PBC clinical outcome could stay in the study without study drug intake. For subjects who declined to stay in the study without study drug intake or who did not participate in the long-term study, a phone call was performed for PBC outcomes on an annual basis until LSLV.

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 study drug. Study visits occurred in clinic, with the assistance of a home health service, or using virtual technologies according to the sites' determination.

Figure 9: Study schedule



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.
Source: Adapted from Protocol Amendment 3.0

- **Study Participants**

Inclusion Criteria

Subjects were required to have met all of the following criteria to be eligible for study participation:

1. Must have given written informed consent and any authorisations required by local law
2. 18 to 75 years old (inclusive)
3. Male or female with a diagnosis of PBC based on any two of the following diagnostic criteria:

   a) History of ALP > 1.0× ULN for at least 6 months

   b) Positive AMA titre (> 1:40 on immunofluorescence or M2 positive by ELISA) or positive PBC-specific ANAs titre

   c) Documented liver biopsy results consistent with PBC

4. 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)
5. 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/1.73m 2 (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 ≥ 100×10 3 /µL

<u>Main Exclusion Criteria</u>

- Advanced PBC as defined by the Rotterdam criteria (albumin below the LLN AND total bilirubin above 1.0× ULN)

- Presence of clinically important hepatic decompensation, including the following:
    a) History of liver transplantation, current placement on liver transplantation list, or current MELD score ≥ 12. 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
    b) Cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma, or hepatorenal syndrome
- Other chronic liver diseases
- History of malignancy diagnosed or treated, actively or within 2 years.
- Treatment with OCA and fibrates 6 weeks prior to screening
- Treatment with colchicine, methotrexate, azathioprine, or long-term systemic corticosteroids (> 2 weeks) during 2 months prior to Screening.
- 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
- For females, pregnancy or breastfeeding
- Immunosuppressant therapies (e.g., cyclosporine, tacrolimus, anti-TNF, or other immune-suppressive biologics)
- Other medications that could affect liver or GI functions,

- **Treatments**

Seladelpar 5 and 10 mg capsules and matching placebo capsules were supplied in a blinded manner. 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. UDCA therapy was continued in those subjects who could tolerate it at their pre-study dose and as recommended per the Investigator's clinical judgment. UDCA was administered orally, 1 or more times per Day. The UDCA dose, compliance with UDCA, and any changes in dose during the study were documented and monitored. Compliance was evaluated by asking the subjects if they missed any doses of UDCA between the visits, and the number of doses missed were recorded.

Any new treatment for PBC symptoms (e.g., antipruritic drugs) was discussed with the Medical Monitor

The following medications were prohibited from use during the study:

- OCA, Fibrates, Colchicine, methotrexate, or azathioprine, Long-term systemic steroids for > 2 weeks, Immunosuppressant therapies (e.g., cyclosporine, tacrolimus, anti-TNF, or other immunosuppressive biologics),

Other medications affecting liver or GI functions, such as absorption of medications, might have been

prohibited and were required to be discussed with the Medical Monitor on a case-by-case basis.

- **Objectives**

The primary objective is to evaluate the treatment effect of seladelpar on composite biochemical improvement in cholestasis markers based on ALP and total bilirubin at 12 months of treatment compared with placebo.

The key secondary objectives are

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

- **Outcomes/endpoints**

Primary endpoint: Proportion of subjects who were considered responders at 12 months based on the following composite endpoint of ALP and total bilirubin:

a) ALP <1.67xULN **and**

b) ≥ 15% decrease in ALP **and**

c) Total bilirubin ≤ 1.0 xULN.

Key secondary endpoints:

- Proportion of subjects with ALP≤ 1.0 x ULN at 12 months (e.g., normalisation)
- Change from baseline in weekly averaged Pruritus NRS in subjects with baseline NRS ≥ 4 at 6 months.

<u>Other Secondary Endpoints</u>
1. Proportion of responders based on the composite endpoint of ALP and total bilirubin at 6 months
2. Proportion of subjects with ALP ≤ 1.0× ULN at 6 months

3. Proportion of subjects with ALP < 1.67× ULN and ALP < 1.5× ULN at 6 and 12 months
4. Absolute and relative changes in ALP at 3, 6, and 12 months
5. Proportion of subjects with a decrease in NRS ≥ 2, NRS ≥ 3, or NRS ≥ 4 in subjects with baseline NRS ≥ 4 at each visit
6. Changes from baseline in Pruritus NRS in subjects with baseline NRS ≥ 4 at 3 and 12 months
7. Change from baseline in QoL measure for use in PBC questionnaire (PBC-40 QoL) at each visit (total score and domain score)
8. Change from baseline in UK-PBC and Global PBC Study Group risk scores at each visit
9. Absolute and relative changes in ALT, AST, GGT, bilirubin (total, direct, and indirect) and 5'-nucleotidase at each visit
10. The first occurrence of PBC clinical outcomes as defined by the following:
a. Overall death
b. Liver transplantation
c. MELD score ≥ 15 for at least 2 consecutive visits
d. Ascites requiring treatment
e. Hospitalisation for new onset or recurrence of any of the following:
– Variceal bleeding
– Hepatic encephalopathy (as defined by a West Haven score ≥ 2)

– Spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis)

Exploratory Endpoints

1. Liver histology changes based on pathology review of biopsy tissues
2. PBC response criteria results (Barcelona, Paris I and II, Toronto I and II, and Rotterdam)
3 Changes from baseline in Pruritus NRS based on additional thresholds for improvement and baseline itch status
4. Changes from baseline in PBC-40 QoL itch domain and the 5-D Itch scale, PGI-C, and PGI-S
5. Absolute and relative changes in lipids, bile acids, sterols, and biomarkers of bile acid synthesis: C4 and FGF19
6. Plasma concentrations of seladelpar and its metabolites (M1, M2, and M3)
7. Absolute and relative changes in markers of inflammation/immune reactivity (e.g., (hs-CRP, fibrinogen, haptoglobin, TNF-alpha, and anti-antibodies)
8. Absolute and relative changes in markers of ELF as measured by liver stiffness using FibroScan®
9. Absolute and relative changes in markers of liver injury: CK18 (M65) and miR-122

- **Sample size**

For the primary efficacy endpoint (the composite biochemical response endpoint of ALP and total bilirubin) evaluated at 12 months, the response rate for placebo group was estimated as 20% and 55% for seladelpar 10 mg dose group. A sample size of 180 subjects was calculated based on a 2-sided test of equality of binomial proportions based on Fisher's exact test with alpha at 0.05 would provide >90% power to detect a difference between 10mg seladelpar and placebo.

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.

Assumptions for the power calculations were based on results from study CB8025-31735. A dropout rate of approximately 10% was assumed for responder analyses.

- **Randomisation and Blinding (masking)**

Subjects were planned to be randomised to receive seladelpar 10 mg or placebo in a 2:1 ratio. Approximately 120 subjects in the seladelpar 10 mg group and 60 subjects in the placebo group were planned. Stratification by ALP level (<350 U/L versus ≥350 U/L) and the presence of clinically important pruritus NRS (<4 versus ≥4) was planned. The randomisation procedure was performed centrally via an interactive web response system (IWRS) at the Day 1 Visit. The randomisation schedule was prepared by an unblinded statistician, separate from the study team.

During the period from randomisation until database lock (dated 30 August 2023), Sponsor study team members responsible for study oversight, subjects, Investigators, and all study-site personnel were blinded to treatment assignment. Clinical event review committee (CERC) and Pathology review committee (PRC) remained blinded to the study treatment. The data safety and monitoring board

(DSMB) reviewed unblinded data as stated in the DSMB charter. The DSMB was composed of 2 external liver disease clinical experts and a biostatistician.

Criteria for emergency unblinding by the PI were outlined in the protocol version 4.0 (09 Feb 2022).

Seladelpar, as well as matched placebo, was supplied in a blinded fashion as 10mg or 5mg (if down-titrated) capsules. Placebo was supplied as capsules identical in appearance to the 5mg and 10mg seladelpar capsules but containing no active medication.

Subjects who met specific safety monitoring criteria in Section 10 of the initial clinical study protocol or had tolerability issues had a dose down-titration. Subjects who were initially assigned to 10 mg were down-titrated to 5 mg in a blinded manner. Subjects who were initially assigned to placebo had a blinded down-titration and remained in the placebo group.

- **Statistical methods**

Analysis sets

The following analysis sets were used for statistical analysis and presentation of data.

All Subjects Screened Analysis Set: defined as all subjects who were screened for enrolment in the study regardless of whether they were enrolled in the study. This set was used for summarizing reasons for screen failures.

Intent-to-treat (ITT) analysis set: defined as any subject who was randomised into the study and receives at least 1 dose of study drug. The ITT analysis set was the primary analysis set used for efficacy analyses, with the exception of secondary endpoints evaluated for subjects with moderate to severe pruritus. Subjects will be analysed according to randomised treatment assignment.

Moderate to severe pruritus NRS (MSPN) analysis set: included any subjects who were in the ITT analysis set who had a baseline NRS value ≥ 4. The MSPN analysis set was the primary analysis set for secondary endpoints based on NRS evaluations. Subjects were analysed according to randomised treatment assignment.

Per-protocol (PP) analysis set: included any subject who were in the ITT analysis set, who had at least 1 postbaseline ALP and total bilirubin evaluation and did not have a protocol violation that was deemed to impact the efficacy analysis. Selected analyses of efficacy were conducted using the PP analysis set. If the PP analysis set differed from the ITT analysis set by less than 5 subjects, then PP analyses would not be performed.

Safety analysis set: included any subject who received at least 1 dose of study drug. Subjects were included in the group based on actual treatment received, if this differed from the treatment assignment. All safety analyses would be completed using the safety analysis set.

Main analysis methods for primary and key secondary endpoints

Primary efficacy endpoints

The primary efficacy endpoint was the proportion of subjects who were considered responders was based on the proportion of subjects achieving the following composite endpoint evaluated at 12 months:

- ALP < 1.67× ULN
- ALP decrease of ≥ 15%
- Total bilirubin ≤ 1.0× ULN

Analyses for the composite endpoint was completed using a Cochran-Mantel-Haenszel (CMH) test. The CMH analysis was stratified by the baseline randomisation stratum (ALP level <350 U/L versus ALP level ≥350 U/L) and was be conducted on the ITT analysis set. The risk difference and 95% CI using Miettinen and Nurminen was also provided. Statistical significance of the difference between placebo and seladelpar was defined as a 2-sided p≤0.05.

Key secondary efficacy endpoint: proportion of subjects with ALP ≤ 1.0× ULN at 12 months (i.e., normalisation)

The key secondary efficacy analysis for the proportion of subjects who achieved normalisation of ALP at 12 months (ALP ≤ 1.0× ULN at 12 months) will be conducted in the ITT analysis set using the same approach specified for the primary efficacy analysis.

Key secondary efficacy endpoint: change from baseline in weekly averaged pruritus NRS at 6 months in subjects with baseline NRS ≥ 4

Change from baseline in weekly averaged pruritus NRS at 6 months was analysed using a mixed-effect model for repeated measures (MMRM) for subjects in the MSPN analysis set. The model included baseline NRS, baseline randomisation stratum (ALP level <350 U/L versus ALP level ≥350 U/L), treatment group, week, and treatment-by-week interaction. The MMRM modelled repeated measures of NRS changes from baseline at relevant timepoints (pre-specified in table 2 in the SAP version 1.0 dated 28-AUG-2023).
Treatment by baseline NRS interaction was explored and added as a term if an interaction was noted to be present (p-value <.05).

LS means for the NRS change from baseline by treatment and the associated standard errors, the LS means for the difference between treatment groups, and the associated 2-sided 95% CIs and 2-sided p-values, were derived from the MMRM model. Significance for this key secondary efficacy analysis was based on the treatment difference at Week 26 (i.e. Month 6). An unstructured covariance matrix was tried first for the MMRM. If the model failed to converge, the following covariance structures would be implemented in order until the model converged: heterogenous Toeplitz, heterogenous compound symmetry, and then compound symmetry. The Kenward-Roger correction for the denominator degrees of freedom would be applied. Observed values and changes from baseline in weekly averaged pruritus NRS were summarised at baseline and by each post-baseline week, as stated in Table 2 of the SAP.

<u>Multiplicity</u>

Study-wide Type I error was maintained at 5% using a hierarchical fixed-sequence methodology for the primary and key secondary efficacy analyses. The fixed-sequence approach for the primary and key secondary analyses was as follows:

- If the primary efficacy analysis was positive for seladelpar 10 mg versus placebo at a 2-sided 0.05 significance level, then the 2 key secondary endpoints would be analysed hierarchically in the following order:

    1. Normalisation of ALP at Month 12 (seladelpar 10 mg versus placebo):
       If negative at a 2-sided 0.05 significance level, no further inferential testing would be performed. Otherwise, if positive, then testing would proceed.
    2. Change from baseline to Month 6 in pruritus NRS (seladelpar 10 mg versus placebo) was evaluated at a 2-sided 0.05 significance level.

Handling of missing data

For the primary endpoint, any subject who did not provide an assessment at, or had discontinued treatment prior to, the specified time point for response evaluation or who otherwise had missing data were considered non responders.
For the second key secondary endpoint, change from baseline in weekly averaged pruritus NRS at 6 months, if a timepoint was missing it would be imputed as an average of the two adjacent weekly averages (at most one week apart); otherwise, it would be imputed by the adjacent weekly average which was present. For example, if a subject in the study was missing Week 23 and Week 24 data, Week 23 would be imputed based on Week 22 average while Week 24 would be imputed based on Week 25 data. Further, a subject who discontinued prior to or during Week 24 would not have an imputed value for Week 26. Data collected after Month 6 was not used for imputation.

Sensitivity analyses

The robustness of the primary analyses was planned to be explored using several sensitivity analyses on a variety of patient populations. Different sensitivity analyses were pre-specified including Complete case analysis, treatment policy strategy, Control-based multiple imputation and tipping point analysis.

Planned subgroup analyses

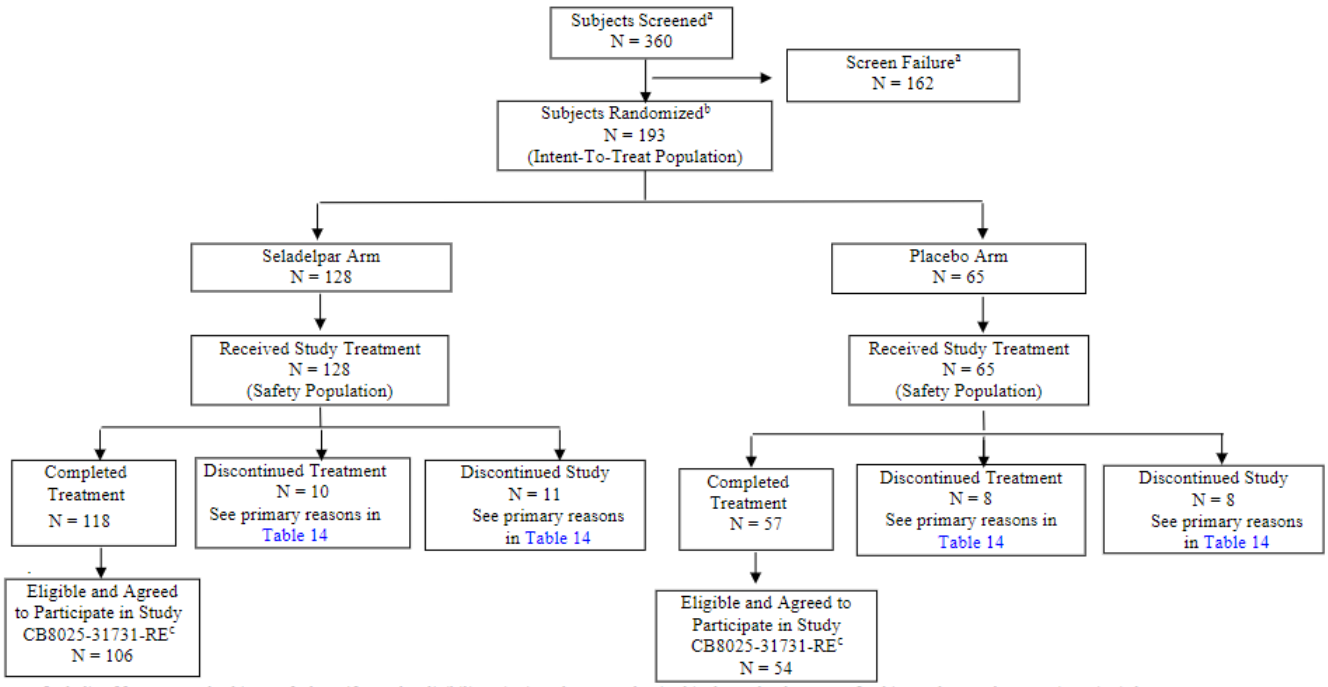
The following subgroup analyses were pre-specified in the SAP. A minimum of 5 subjects in each treatment group were required to conduct subgroup analyses.

- Age categories (age at screening: <65, ≥65 years; age at PBC diagnosis <50, ≥50 years)
- Sex (Female, Male)
- Race (White, Black, Asian, Other)
- Region (North America, Europe, Rest-of-World)
- Baseline ALP (< 350 U/L, ≥ 350 U/L)
- Total bilirubin (TB) (< 0.6 × ULN, ≥ 0.6 × ULN)
- Pruritus NRS (< 4, ≥ 4)
- UDCA use vs UDCA intolerance
- Prior use of OCA and/or fibrates (yes, no)
- Cirrhosis (yes, no)
- TB (≤ 1 × ULN, > 1 × ULN)

The consistency of the treatment effects across stratification levels were planned to be assessed using the same approach as specified for the primary efficacy analysis. Subgroup analyses for ALP would not be stratified or adjusted by ALP stratum; subgroup analysis for pruritus NRS were performed similarly.

Results

- **Participant flow**



[a] Including 23 re-screened subjects, of whom 12 met the eligibility criteria and were randomized in the study; there were 5 subjects who met the screening criteria but were not enrolled in the study.
[b] Subjects were randomized in a 2:1 ratio to receive seladelpar or placebo.
[c] Russian subjects (9 subjects in total including 8 in the seladelpar arm and 1 in the placebo arm) were not eligible for study CB8025-31731-RE due to operational complexities (see Section 9.9.1.5).
Sources: Tables 14.1.1, 14.1.2, 14.1.3.1.1, and 14.1.3.2.1

Table 21: Subject disposition (ITT population)

	Placebo (N = 65) n (%)	Seladelpar 10 mg (N = 128) n (%)	Total (N = 193) n (%)
Subjects Randomized and Treated	65 (100.0)	128 (100.0)	193 (100.0)
Subjects Who Completed Treatment	57 (87.7)	118 (92.2)	175 (90.7)
Subjects Who Discontinued Treatment[a]	8 (12.3)	10 (7.8)	18 (9.3)
Primary Reason for Treatment Discontinuation			
Adverse Event	4 (6.2)	4 (3.1)	8 (4.1)
Liver Safety Monitoring	1 (1.5)	2 (1.6)	3 (1.6)
Muscle Safety Monitoring	0	0	0
Serum Creatinine Monitoring	0	0	0
Pancreatic Safety Monitoring	0	0	0
AEs Other than Monitoring Criteria	3 (4.6)	2 (1.6)	5 (2.6)
PBC Clinical Outcome[b]	0	0	0
Entered the Study in Violation of this Protocol	0	0	0
Required the use of Prohibited Concomitant Medications	0	0	0
Withdrawal of Informed Consent	2 (3.1)	4 (3.1)	6 (3.1)
Discretion of the Investigator for Medical Reasons	0	0	0
Pregnancy	0	0	0
Discretion of the Investigator/Sponsor, Subject Noncompliance	0	0	0
Significant Protocol Deviation	1 (1.5)	1 (0.8)	2 (1.0)
Administrative Decision by PI, Sponsor or Designee	0	0	0
Lost to Follow-Up	1 (1.5)	1 (0.8)	2 (1.0)
Death	0	0	0
Other	0	0	0
Subjects Who Completed Study	57 (87.7)	117 (91.4)	174 (90.2)
Subjects Who Discontinued Study	8 (12.3)	11 (8.6)	19 (9.8)
Primary Reason for Study Discontinuation			
Adverse Event	4 (6.2)	3 (2.3)	7 (3.6)
PBC Clinical Outcome[b]	0	0	0
Death	0	0	0
Lack of Efficacy	0	0	0
Lost To Follow-Up	1 (1.5)	1 (0.8)	2 (1.0)
Non-Compliance with Study Drug	0	0	0

Physician Decision	0	0	0
Pregnancy	0	0	0
Protocol Deviation	1 (1.5)	1 (0.8)	2 (1.0)
Study Site Terminated by Sponsor	0	0	0
Study Terminated by Sponsor	0	0	0
Technical Problem	0	0	0
Withdrawal By Subject	2 (3.1)	5 (3.9)	7 (3.6)
Other	0	1 (0.8)	1 (0.5)
Subjects Who Agreed to Participate in CB8025-31731-RE Study	54 (83.1)	110 (85.9)	164 (85.0)
Subjects Eligible for CB8025-31731-RE Who Completed Treatment[c]	56 (86.2)	110 (85.9)	166 (86.0)
Eligible Subjects Who Completed Treatment and Agreed to Participate in CB8025-31731-RE[c,d]	54 (96.4)	106 (96.4)	160 (96.4)
Subjects Who Declined to Participate in CB8025-31731-RE Study	11 (16.9)	18 (14.1)	29 (15.0)
Subjects Who Completed Treatment and Completed Follow up Period	3 (4.6)	7 (5.5)	10 (5.2)
Subjects Who Completed Treatment and did not Complete Follow up Period	0	1 (0.8)	1 (0.5)

Abbreviations: ITT = intent-to-treat; PBC = primary biliary cholangitis; PI = principal investigator
Percentages were based on the number of subjects in the All Randomized Subjects Set.
Subjects 219-402, 340-402, 340-403, 342-401, and 342-403 agreed to participate in CB8025-31731-RE Study and also completed their Follow-up visit.
[a] One subject (406-401) in the seladelpar arm discontinued treatment early but remained on study (see Section 12.3.1.3.3).
[b] One subject (605-401) in the seladelpar arm had a PBC clinical outcome event 7 days after completion of the study treatment period (see Section 11.8.4.5).
[c] Russian subjects were not eligible for CB8025-31731-RE.
[d] Percentages were based on the number of subjects eligible for CB8025-31731-RE who completed treatment.
Source: Tables 14.1.3.1.1 and 14.1.3.2.1

- **Recruitment**

Study period: 21 April 2021 (first subject randomised) – 11 August 2023 (last subject last visit)

- **Conduct of the study**

The study had 3 protocol amendments, none which had any impact on the study integrity.

There were 53.9% protocol deviations in the seladelpar group and 50.8% in the placebo group. The most common significant protocol or ICH/GCP deviations on study were related to study treatment administration/dispensing (20.7%), study procedures/assessments (17.6%), ICF process/timing (13%), visit scheduling (13%), and study treatment compliance (10.9%). A higher percentage of subjects in the placebo arm had visit scheduling deviations relative to the seladelpar arm (18.5% vs 10.2%, respectively), and a higher percentage of subjects in the seladelpar arm had study treatment randomisation deviations relative to the placebo arm (8.6% vs 1.5%, respectively). A total of 3 subjects had significant protocol deviations that led to their exclusion from the PP Analysis Set (2 placebo patients, one with gilberts syndrome and elevated bilirubin levels, one with concomitant UDCA intake, who were re-started on UDCA during the study and 1 seladelpar patient with concomitant OCA treatment.

- **Baseline data**

Table 22: Subject demographics (ITT analysis set)

	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	Total (N = 193)
Age at Screening (years)			
Mean (SD)	57.0 (9.17)	56.6 (9.99)	56.7 (9.70)
Min, Max	33, 75	28, 75	28, 75
< 65 years, n (%)	53 (81.5)	99 (77.3)	152 (78.8)
≥ 65 years n (%)	12 (18.5)	29 (22.7)	41 (21.2)
Sex, n (%)			
Female	60 (92.3)	123 (96.1)	183 (94.8)
Male	5 (7.7)	5 (3.9)	10 (5.2)
Race[a], n (%)			
American Indian or Alaska Native	3 (4.6)	3 (2.3)	6 (3.1)
Asian	4 (6.2)	7 (5.5)	11 (5.7)
Black or African American	2 (3.1)	2 (1.6)	4 (2.1)
Native Hawaiian or Other Pacific Islander	0	0	0
White	56 (86.2)	114 (89.1)	170 (88.1)
Multiple	0	0	0
Other	0	0	0
Declined to Answer	0	0	0
Missing	0	2 (1.6)	2 (1.0)
Ethnicity, n (%)			
Hispanic or Latino	27 (41.5)	29 (22.7)	56 (29.0)
Not Hispanic or Latino	38 (58.5)	97 (75.8)	135 (69.9)
Declined to Answer	0	0	0
Missing	0	2 (1.6)	2 (1.0)
Region, n (%)			
North America	13 (20.0)	50 (39.1)	63 (32.6)
Latin America	19 (29.2)	24 (18.8)	43 (22.3)
EMEA	27 (41.5)	49 (38.3)	76 (39.4)
APAC	6 (9.2)	5 (3.9)	11 (5.7)
Weight[b] (kg)			
Mean (SD)	69.9 (13.94)	71.7 (15.94)	71.1 (15.28)
Min, Max	44.0, 105.9	40.6, 127.5	40.6, 127.5
BMI[b,c] (kg/m^2)			
Mean (SD)	26.83 (4.811)	27.24 (5.615)	27.10 (5.348)
Min, Max	17.4, 40.1	17.5, 45.0	17.4, 45.0

Abbreviations: APAC = Asia-Pacific; BMI = body mass index; EMEA = Europe, the Middle East and Africa; ITT = intent-to-treat

Percentages were based on the number of subjects in the ITT Analysis Set under each treatment arm.
N = total number of subjects, n = number of subjects in the category

[a] Race and ethnicity were not collected for subjects enrolled in France due to prohibition by local regulations.
[b] The baseline measurement was the last non-missing assessment evaluated prior to the first administration of study drug.
[c] BMI = weight in kg / height in m^2

Source: Table 14.1.5.1.1

Table 23: Baseline disease characteristics (ITT analysis set)

Baseline Characteristics	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	Total (N = 193)
Duration of PBC (years)[a], n	65	128	193
Mean (SD)	8.6 (6.46)	8.2 (6.70)	8.3 (6.60)
Min, Max	0.4, 27.0	0.2, 33.0	0.2, 33.0
Age at Diagnosis of PBC (years) [b], n	65	128	193
Mean (SD)	49.3 (10.94)	49.2 (9.94)	49.2 (10.26)
Min, Max	26, 68	25, 70	25, 70
< 50, n (%)	32 (49.2)	61 (47.7)	93 (48.2)
≥ 50, n (%)	33 (50.8)	67 (52.3)	100 (51.8)
AMA Status[c], n (%)			
Positive	55 (84.6)	106 (82.8)	161 (83.4)
Negative	9 (13.8)	20 (15.6)	29 (15.0)
Equivocal	1 (1.5)	2 (1.6)	3 (1.6)
Rotterdam Stage of Disease[d]			
Mild	60 (92.3)	106 (82.8)	166 (86.0)
Moderately Advanced	5 (7.7)	22 (17.2)	27 (14.0)
Advanced	0	0	0
MELD Score, n	65	128	193
Mean (SD)	6.7 (0.93)	6.8 (0.97)	6.8 (0.96)
Min, Max	6.0, 11.0	6.0, 11.7	6.0, 11.7
Subjects with Cirrhosis at Baseline, n (%)	9 (13.8)	18 (14.1)	27 (14.0)
Child-Pugh Class CP-A[c]	9 (100.0)	18 (100.0)	27 (100.0)
Subjects With PHT	3 (4.6)	0	3 (1.6)
Subjects Without PHT	62 (95.4)	128 (100.0)	190 (98.4)
Liver Stiffness by FibroScan[e] (kPa), m	62	115	177
Mean (SD)	8.7 (4.18)	9.8 (6.16)	9.5 (5.56)
Min, Max	3.8, 23.0	3.1, 43.2	3.1, 43.2
Fibrosis Score Derived from Liver Stiffness[f], m	62	115	177
F0, n/m (%)	26 (41.9%)	44 (38.3%)	70 (39.5%)
F1, n/m (%)	15 (24.2%)	22 (19.1%)	37 (20.9%)
F2, n/m (%)	7 (11.3%)	17 (14.8%)	24 (13.6%)
F3, n/m (%)	10 (16.1%)	21 (18.3%)	31 (17.5%)
F4, n/m (%)	4 (6.5%)	11 (9.6%)	15 (8.5%)
Enhanced Liver Fibrosis (ELF) Score, n	65	128	193
Mean (SD)	10.2 (0.85)	10.2 (1.03)	10.2 (0.97)
Min, Max	8.6, 12.3	8.1, 13.3	8.1, 13.3
Duration of Prior UDCA Usage[g] (years), n	65	128	193
Mean (SD)	7.8 (6.24)	7.3 (6.46)	7.4 (6.37)
Min, Max	0.0, 28.0	0.0, 33.0	0.0, 33.0
UDCA Intolerance[h], n (%)			

Baseline Characteristics	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	Total (N = 193)
Yes	4 (6.2)	8 (6.3)	12 (6.2)
No	61 (93.8)	120 (93.8)	181 (93.8)
Total Daily UDCA Dose at Baseline[i] (mg/kg), n	61	120	181
Mean (SD)	14.9 (3.30)	15.0 (3.08)	15.0 (3.15)
Min, Max	6.5, 22.7	7.2, 23.6	6.5, 23.6
Prior Use of OCA and/or Fibrates, n (%)			
Yes	13 (20.0)	20 (15.6)	33 (17.1)
No	52 (80.0)	108 (84.4)	160 (82.9)
Pruritus NRS, n	65	128	193
Mean (SD)	3.0 (2.96)	3.0 (2.81)	3.0 (2.85)
Min, Max	0, 9	0, 9	0, 9
< 4	42 (64.6)	79 (61.7)	121 (62.7)
≥ 4	23 (35.4)	49 (38.3)	72 (37.3)
Pruritus NRS for subjects with baseline Pruritus NRS ≥ 4, n	23	49	72
Mean (SD)	6.6 (1.44)	6.1 (1.42)	6.3 (1.43)
Min, Max	4, 9	4, 9	4, 9
UK-PBC Risk Score			
5 years, n	65	125	190
Mean (SD)	0.022 (0.018)	0.023 (0.019)	0.022 (0.018)
Min, Max	0.002, 0.083	0.004, 0.093	0.002, 0.093
10 years, n	65	125	190
Mean (SD)	0.071 (0.056)	0.072 (0.057)	0.072 (0.057)
Min, Max	0.007, 0.252	0.013, 0.280	0.007, 0.280
15 years, n	65	125	190
Mean (SD)	0.125 (0.093)	0.128 (0.096)	0.127 (0.095)
Min, Max	0.013, 0.417	0.024, 0.457	0.013, 0.457
GLOBE Score, n	65	125	190
Mean (SD)	0.33 (0.708)	0.31 (0.660)	0.32 (0.675)
Min, Max	-1.3, 1.8	-1.2, 1.8	-1.3, 1.8

Abbreviations: AMA = anti-mitochondrial antibodies; CP = Child-Pugh; ITT = intent-to-treat; kPa = kilopascals; MELD = model for end-stage liver disease; NRS = numerical rating scale; OCA = obeticholic acid; PBC = primary biliary cholangitis; PHT = portal hypertension; UDCA = ursodeoxycholic acid; UK = United Kingdom.
N = total number of subjects, n = number of subjects in the category

Percentages were based on the number of subjects in the ITT Analysis Set under each treatment arm, except for FibroScan[e] where the number of subjects with procedure performed was used as the denominator (denoted with 'm').
The baseline measurement was the last non-missing measurement prior to the first administration of study drug, unless otherwise specified. Baseline measurements for chemistry and hematology measures, and other laboratory quantitative measures were

defined as the arithmetic mean of applicable measurements at Screening, Run-in, Day 1, and unscheduled assessments prior to or on Day 1. Baseline Pruritus NRS was defined as the mean of all daily recorded scores during the Run-in Period and on Day 1.

[a] Duration of PBC (time [in years] from diagnosis date to the informed consent date) was defined as (informed consent date – PBC diagnosis date + 1) / 365.2425.
[b] Age at PBC diagnosis (years) was calculated as year of PBC diagnosis – year of birth.
[c] Defined by reactivity against the mitochondrial M2 antibody.
[d] Mild: normal total bilirubin and normal albumin; Moderately Advanced: abnormal albumin or abnormal total bilirubin; Advanced: abnormal albumin and abnormal total bilirubin.
[e] Percentages for baseline Child-Pugh score were based on subjects with cirrhosis at baseline.
[f] The cut-off values for F1, F2, F3, and F4 were 7.1, 8.8, 10.7 and 16.9 kPa, respectively.
[g] Duration of prior UDCA usage (years) = (End Date – Start Date of UDCA usage in PBC treatment history + 1) / 365.2425.
[h] UDCA intolerance was from UDCA usage at baseline.
[i] Total Daily UDCA Dose (mg/kg) = Total Daily UDCA Dose (mg) at Baseline/Day 1 Weight (kg).

Source: Tables 14.1.5.2.1 and 14.1.6.2.1

Table 24: Baseline laboratory values (ITT analysis set)

Subject Characteristic	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	Total (N = 193)
ALP (U/L), n; (reference range: 37-116)	65	128	193
Mean (SD)	313.8 (117.68)	314.6 (122.96)	314.3 (120.90)
Min, Max	161, 698	182, 786	161, 786
< 350, n (%)	47 (72.3)	93 (72.7)	140 (72.5)
≥ 350, n (%)	18 (27.7)	35 (27.3)	53 (27.5)
Total Bilirubin (mg/dL), n; (reference range: 0.1-1.10)	65	128	193
Mean (SD)	0.737 (0.310)	0.769 (0.314)	0.758 (0.312)
Min, Max	0.26, 1.95	0.31, 1.88	0.26, 1.95
≤ 1× ULN, n (%)	60 (92.3)	108 (84.4)	168 (87.0)
> 1 and ≤ 2× ULN, n (%)	5 (7.7)	20 (15.6)	25 (13.0)
> 2× ULN, n (%)	0	0	0
< 0.6× ULN, n (%)	32 (49.2)	59 (46.1)	91 (47.2)
≥ 0.6× ULN, n (%)	33 (50.8)	69 (53.9)	102 (52.8)
Direct Bilirubin (mg/dL), n; (reference range: 0.00-0.20)	65	128	193
Mean (SD)	0.211 (0.142)	0.236 (0.161)	0.227 (0.155)
Min, Max	0.06, 0.83	0.07, 0.92	0.06, 0.92
ALT (U/L), n; (reference range: 6-41)	65	128	193
Mean (SD)	48.2 (22.83)	47.4 (23.47)	47.7 (23.20)
Min, Max	9, 115	13, 109	9, 115
AST (U/L), n; (reference range: 9-34)	65	128	193
Mean (SD)	41.7 (16.03)	39.6 (16.14)	40.3 (16.09)
Min, Max	16, 84	16, 94	16, 94
GGT (U/L), n; (reference range: 7-38)	65	128	193
Mean (SD)	287.5 (249.56)	269.0 (240.04)	275.3 (242.79)
Min, Max	42, 1088	13, 1402	13, 1402
Albumin (g/dL), n; (reference range: 3.50-5.50)	65	128	193
Mean (SD)	4.1 (0.23)	4.2 (0.27)	4.1 (0.26)
Min, Max	3.6, 4.6	3.0, 4.8	3.0, 4.8
Platelet (10^3/uL), n; (reference range: 140-400)	65	125	190
Mean (SD)	241.9 (84.46)	241.7 (78.87)	241.7 (80.60)
Min, Max	103, 506	90, 477	90, 506
INR, n; (reference range: 0.8-1.2)	65	128	193
Mean (SD)	1.0 (0.09)	1.0 (0.08)	1.0 (0.09)

Min, Max	0.9, 1.5	0.8, 1.3	0.8, 1.5
Total Cholesterol (mg/dL), n; (reference range: 100-200)	65	128	193
Mean (SD)	236.8 (55.10)	240.8 (51.29)	239.5 (52.49)
Min, Max	128, 409	142, 382	128, 409
LDL-C (mg/dL), n; (reference range: 50-130)	65	128	193
Mean (SD)	137.4 (51.13)	136.7 (45.35)	137.0 (47.24)
Min, Max	51, 295	54, 268	51, 295
HDL-C (mg/dL), n; (reference range: 35-60)	65	128	193
Mean (SD)	75.1 (22.34)	80.5 (23.09)	78.7 (22.93)
Min, Max	34, 126	34, 165	34, 165

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; HDL-C = high density lipoprotein cholesterol; INR = international normalized ratio; ITT = intent-to-treat LDL-C = low density lipoprotein cholesterol; ULN = upper limit of normal
N = total number of subjects, n = number of subjects in the category
Percentages were based on the number of subjects in the ITT Analysis Set under each treatment arm.
Baseline measurements for chemistry and hematology measures, and other laboratory quantitative measures were defined as the arithmetic mean of applicable measurements at Screening, Run-in, Day 1, and unscheduled assessments prior to or on Day 1.
Source: Table 14.1.5.2.1

Table 25: PBC medical history (ITT analysis set)

	Placebo (N = 65) n (%)	**Seladelpar 10 mg (N = 128) n (%)**	**Total (N = 193) n (%)**
Esophageal Varices[a]	0	1 (0.8)	1 (0.5)
History of Pruritus	48 (73.8)	91 (71.1)	139 (72.0)
Location of Pruritus			
Generalized	32 (49.2)	69 (53.9)	101 (52.3)
Localized	16 (24.6)	22 (17.2)	38 (19.7)
Pruritus Treated (Yes)	20 (30.8)	33 (25.8)	53 (27.5)
Fatigue (Yes)	33 (50.8)	60 (46.9)	93 (48.2)
Prior Medication(s)[b] for PBC			
UDCA	65 (100.0)	128 (100.0)	193 (100.0)
OCA	10 (15.4)	15 (11.7)	25 (13.0)
Fibrates	5 (7.7)	7 (5.5)	12 (6.2)
Steroids	1 (1.5)	3 (2.3)	4 (2.1)
Immunosuppressant	0	0	0
Methotrexate	0	2 (1.6)	2 (1.0)
Systemic Steroids	1 (1.5)	0	1 (0.5)
Colchicine	0	0	0
Other	2 (3.1)	0	2 (1.0)

Abbreviations: ITT = intend-to-treat; OCA = obeticholic acid; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic Acid
N = total number of subjects, n = number of subjects in the category
Percentages were based on the number of subjects in the Intent-To-Treat Analysis Set under each treatment arm.
[a] A protocol deviation was documented for 1 subject who enrolled with a medical history of Esophageal varices.
[b] A subject may have taken more than one medication.
Source: Table 14.1.6.2.1

Table 26: Concomitant medications used by ≥ 10% of subjects in any treatment arm (safety analysis set)

WHODD Preferred Term	Placebo (N = 65) n (%)	Seladelpar 10 mg (N = 128) n (%)	Total (N = 193) n (%)
Subjects Receiving Medications on Study	64 (98.5)	125 (97.7)	189 (97.9)
Paracetamol	22 (33.8)	27 (21.1)	49 (25.4)
Omeprazole	11 (16.9)	26 (20.3)	37 (19.2)
Colecalciferol	15 (23.1)	25 (19.5)	40 (20.7)
Vitamin D NOS	3 (4.6)	18 (14.1)	21 (10.9)
Ibuprofen	12 (18.5)	16 (12.5)	28 (14.5)
Levothyroxine	7 (10.8)	14 (10.9)	21 (10.9)
Hydroxyzine	3 (4.6)	14 (10.9)	17 (8.8)
Atorvastatin	12 (18.5)	11 (8.6)	23 (11.9)
Colestyramine	8 (12.3)	6 (4.7)	14 (7.3)
Acetylsalicylic acid	7 (10.8)	5 (3.9)	12 (6.2)

Abbreviation: NOS = not otherwise specified; WHODD = World Health Organization Drug Dictionary
N = total number of subjects, n = number of subjects in the category
Data were sorted by descending frequency in preferred terms in the seladelpar 10 mg arm and then placebo arm, if applicable.
Concomitant medications were coded using WHO Drug dictionary version March 2021 format B3.

- **Numbers analysed**

Table 27: Analysis sets

	Placebo (N = 65) n (%)	Seladelpar 10 mg (N = 128) n (%)	Total (N = 193) n (%)
Intent-to-Treat Analysis Set[a]	65 (100)	128 (100)	193 (100)
Moderate to Severe Pruritus NRS Analysis Set[b]	23 (35.4)	49 (38.3)	72 (37.3)
Per-protocol Analysis Set[c]	63 (96.9)	127 (99.2)	190 (98.4)
Biopsy Analysis Set[d]	18 (27.7)	35 (27.3)	53 (27.5)
Safety Analysis Set[e]	65 (100)	128 (100)	193 (100)
Pharmacokinetics Analysis Set[f]	0	71 (55.5)	71 (36.8)

- **Outcomes and estimation**

Primary efficacy endpoint

Table 28: 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.
Source: Table 14.2.1.1

Since the Breslow-Day p-value assessing homogeneity of treatment effect across stratum was < 0.05, the study drug treatment effect was analysed for each stratum (see table below). The results from the stratum analyses were consistent with those of the primary analysis of the primary efficacy endpoint showing a higher percentage of responders in the seladelpar arm compared with the placebo arm, with the exception of one stratum in the setting of a small sample size. 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: the response rate was 13.3% (2 out of 15 subjects) in the seladelpar arm and 22.2% (2 out of 9 subjects) in the placebo arm. The applicant states that the differences in responses in subjects in this stratum should be interpreted considering its small sample size as well as the requirement for greater reductions in ALP for subjects in this stratum having markedly elevated ALP values at baseline to achieve the ALP < 1.67× ULN component of the composite biochemical response endpoint.

Table 29: Analysis of composite endpoint response rate at month 12 by stratum intent-to-treat analysis set

Stratum 1: ALP < 350 U/L, Pruritus NRS < 4	Placebo (N=65)	Seladelpar 10 mg (N=128)
Subjects who Achieved Response at Month 12, n/m (%) [a] [b] Wald 95% CI for Response Rate	7/ 33 (21.2) (7.3, 35.2)	51/ 64 (79.7) (69.8, 89.5)
Risk Difference (%) (Wald 95% CI) Pearson's chi-squared test p-value		58.5 (41.4, 75.6) < 0.0001
At least one expected cell count < 5 [c] Risk Difference (%) (Exact 95% CI) Fisher's exact test p-value		No

Stratum 2: ALP < 350 U/L, Pruritus NRS >= 4	Placebo (N=65)	Seladelpar 10 mg (N=128)
Subjects who Achieved Response at Month 12, n/m (%) [a] [b] Wald 95% CI for Response Rate	4/ 14 (28.6) (4.9, 52.2)	20/ 29 (69.0) (52.1, 85.8)
Risk Difference (%) (Wald 95% CI) Pearson's chi-squared test p-value		40.4 (11.4, 69.4) 0.0124
At least one expected cell count < 5 [c] Risk Difference (%) (Exact 95% CI) Fisher's exact test p-value		No

Stratum 3: ALP >= 350 U/L, Pruritus NRS < 4	Placebo (N=65)	Seladelpar 10 mg (N=128)
Subjects who Achieved Response at Month 12, n/m (%) [a] [b] Wald 95% CI for Response Rate	2/ 9 (22.2) (0.0, 49.4)	2/ 15 (13.3) (0.0, 30.5)
Risk Difference (%) (Wald 95% CI) Pearson's chi-squared test p-value		-8.9 (-41.0, 23.3) 0.5716
At least one expected cell count < 5 [c] Risk Difference (%) (Exact 95% CI) Fisher's exact test p-value		Yes -8.9 (-48.2, 25.7) 0.6146

Stratum 4: ALP >= 350 U/L, Pruritus NRS >= 4	Placebo (N=65)	Seladelpar 10 mg (N=128)
Subjects who Achieved Response at Month 12, n/m (%) [a] [b] Wald 95% CI for Response Rate	0/ 9 (0.0, 0.0)	6/ 20 (30.0) (9.9, 50.1)
Risk Difference (%) (Wald 95% CI) Pearson's chi-squared test p-value		30.0 (9.9, 50.1) 0.0650
At least one expected cell count < 5 [c] Risk Difference (%) (Exact 95% CI) Fisher's exact test p-value		Yes 30.0 (-6.4, 54.3) 0.1375

Table 30: Sensitivity analysis of composite biochemical response at month 12 (complete case and treatment policy strategy) (ITT analysis set)

	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	Risk Difference (Miettinen-Nurminen 95% CI)	CMH test p-value[b]
	Composite Endpoint Response Rate[a] n (%)			
Complete Case Analysis[c], n/m (%)	13 / 57 (22.8)	79 / 114 (69.3)	46.5 (31.4, 58.9)	p < 0.0001
Treatment Policy Strategy Analysis[d], n/N (%)	13 / 65 (20.0)	80[e] / 128 (62.5)	42.5 (28.5, 54.2)	p < 0.0001

Abbreviations: ALP = alkaline phosphatase; CMH = Cochran-Mantel-Haenszel; ITT= intent-to-treat; NRS = numerical rating scale; ULN = upper limit of normal

N = total number of subjects, n/m (%) = (number of responders/number of subjects who have assessment at Month 12) x 100%

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

[b] 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.

[c] Subjects with missing data at Month 12 were excluded from analysis.

[d] Data collected following treatment discontinuation were included in data summaries or inferential analyses.

[e] Subject [redacted] had laboratory assessments 27 days after last treatment date and was classified as a responder.

Source: Tables 14.2.1.3 and 14.2.1.4 and Listing 16.2.6.1

Table 31: Sensitivity analysis of composite biochemical response at month 12 (control-based multiple imputation) (ITT analysis set)

Control-based Multiple Imputation[a]	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	CMH test p-value[b]
Observed Cases, n (%)	57 (87.7)	114 (89.1)	p < 0.0001
Subjects Requiring Imputation, n (%)[a]	8 (12.3)	14 (10.9)	

Abbreviation: ALP = alkaline phosphatase; CMH = Cochran-Mantel-Haenszel; ITT= intent-to-treat

N = total number of subjects. n = number of subjects in the category

[a] Missing ALP and total bilirubin results at Month 12 were imputed with a control-based multiple imputation method, and then used to classify a subject as a responder or a nonresponder.

[b] Two-sided p-value for pair-wise comparison was based on combining the CMH test results out of 100 multiple imputed datasets.

Source: Table 14.2.1.5

Key Secondary Efficacy Endpoints:

Table 32: Analysis of normalisation of ALP response rate at month 12 (ITT analysis set)

	Placebo (N = 65)	**Seladelpar 10 mg (N = 128)**
Subjects with ALP ≤ 1.0× ULN at Month 12[a,b], n (%) Wald 95% CI for response rate	0 (0.0, 0.0)	32 (25.0) (17.5, 32.5)
Risk difference (Miettinen-Nurminen 95% CI)		25.0 (18.3, 33.2)
Cochran-Mantel-Haenszel test p-value[c]		< 0.0001
Mantel-Fleiss criterion[c]		10.8
Breslow-Day p-value[c]		NE

Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; ITT = intent-to-treat; n = number of subjects in each category; N = total number of subjects; NE = not estimable; ULN = upper limit of normal.

[a] A subject was designated as a responder if the ALP value at Month 12 was < 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 Cochran-Mantel-Haenszel test adjusted for both randomisation 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. Mantel-Fleiss criterion was used to assess the validity of the chi-square approximation for the distribution of the Mantel-Haenszel statistic.

Source: CSR CB8025-32048 Table 14.2.3.1.

Table 33: MMRM analysis of change from baseline to month 6 in weekly averaged pruritus NRS (MSPN analysis set)

Visit	**Placebo (N = 23)**	**Seladelpar 10 mg (N = 49)**
Baseline, n	23	49
Mean (SD)	6.6 (1.44)	6.1 (1.42)
Median	7.1	5.9
Q1, Q3	5.6, 7.7	4.9, 7.4
Minimum, maximum	4, 9	4, 9
Month 6 change from baseline[a], n	20	45
Mean (SD)	-1.9 (1.96)	-3.1 (2.07)
Median	-1.9	-2.9
Q1, Q3	-3.3, -0.4	-4.4, -2.0
Minimum, maximum	-6, 1	-8, 2
LS mean (SE)[b]	-1.7 (0.41)	-3.2 (0.28)
LS mean of difference (95% CI)		-1.5 (-2.5, -0.5)
p-value		0.0047

Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; LS = least squares; MMRM = mixed-effect model repeated measure; MSPN = moderate to severe pruritus numerical rating scale; n = number of subjects with nonmissing or imputed results at a specific timepoint; N = total number of subjects; NRS = numerical rating scale; SD = standard deviation; SE = standard error.

[a] Missing assessment at specific timepoint was imputed as an average of the 2 adjacent weekly averages (at most one week apart): if only one adjacent weekly average was available, it was imputed by the available adjacent weekly average; if no adjacent weekly average was available, it was not imputed.

[b] Change from baseline was estimated by MMRM model including terms for baseline NRS, stratification variables (baseline ALP level < 350 U/L versus ALP level ≥ 350 U/L), treatment arm, week, and treatment-by-week interaction. Unstructured covariance was applied for the repeated measure, and Kenward-Roger correction was applied for the denominator degrees of freedom.

The MSPN analysis set included subjects in the intent-to-treat analysis set who had a baseline NRS value ≥ 4.

Source: CSR CB8025-32048 Table 14.2.5.1.

Other secondary endpoints related to the biomarkers of the primary endpoint:

Figure 10: Composite biochemical response over time (ITT analysis set)

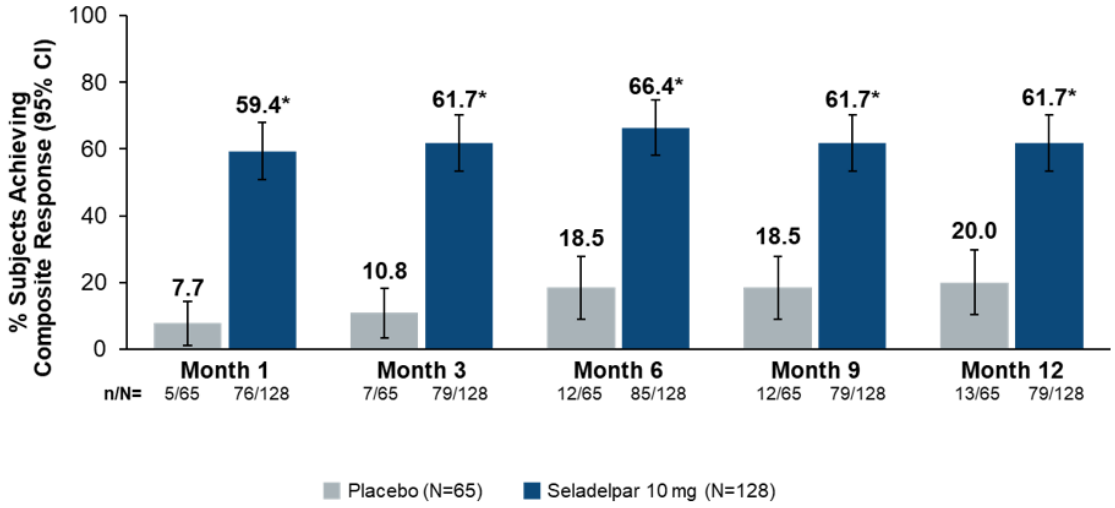
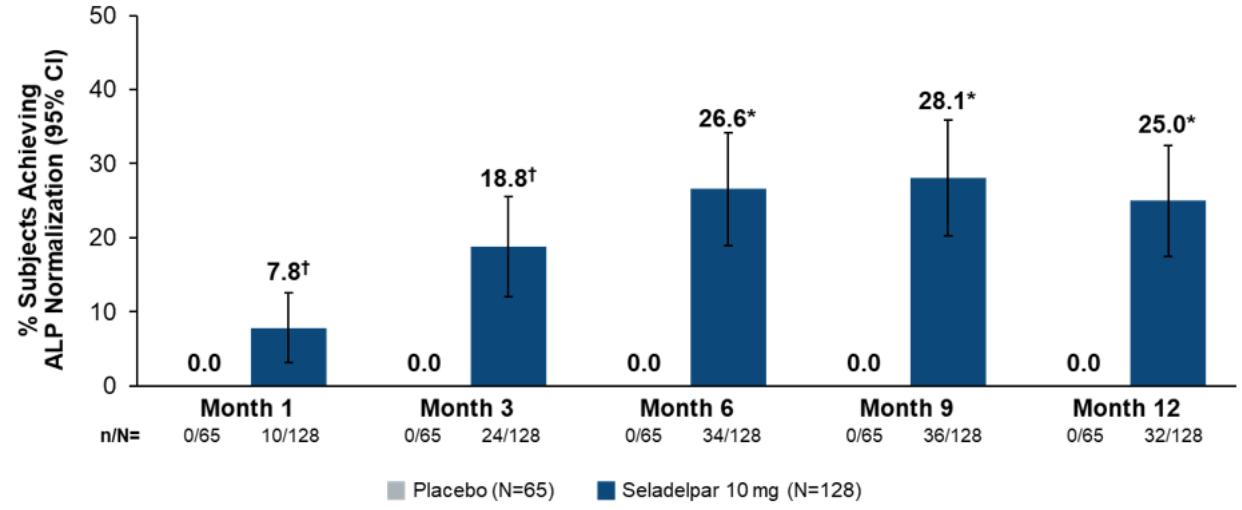


Figure 11: Percentage of subjects achieving normalisation of ALP over time (ITT analysis set)



Proportion of Subjects with ALP < 1.67× ULN and ALP < 1.5× ULN at Months 6 and 12

The effects of seladelpar on the proportion of subjects with ALP < 1.67× ULN and ALP < 1.5× ULN at Months 6 and 12 were analysed as secondary endpoints using the same approach as that described for the key secondary efficacy endpoint of ALP normalisation at Month 12. At Month 6, there was a higher percentage of subjects with ALP < 1.67× ULN and ALP < 1.5× ULN in the seladelpar arm (69.5% and 64.1%, respectively), compared with the placebo arm (23.1% and 12.3%, respectively). Similarly, at Month 12, higher percentages of subjects with ALP < 1.67× ULN and ALP < 1.5× ULN were observed in the seladelpar arm (65.6% and 58.6%, respectively), compared with the placebo arm (26.2% and 12.3%, respectively).

Figure 12: Percent change from baseline and mean values of ALP over time (ITT analysis set)

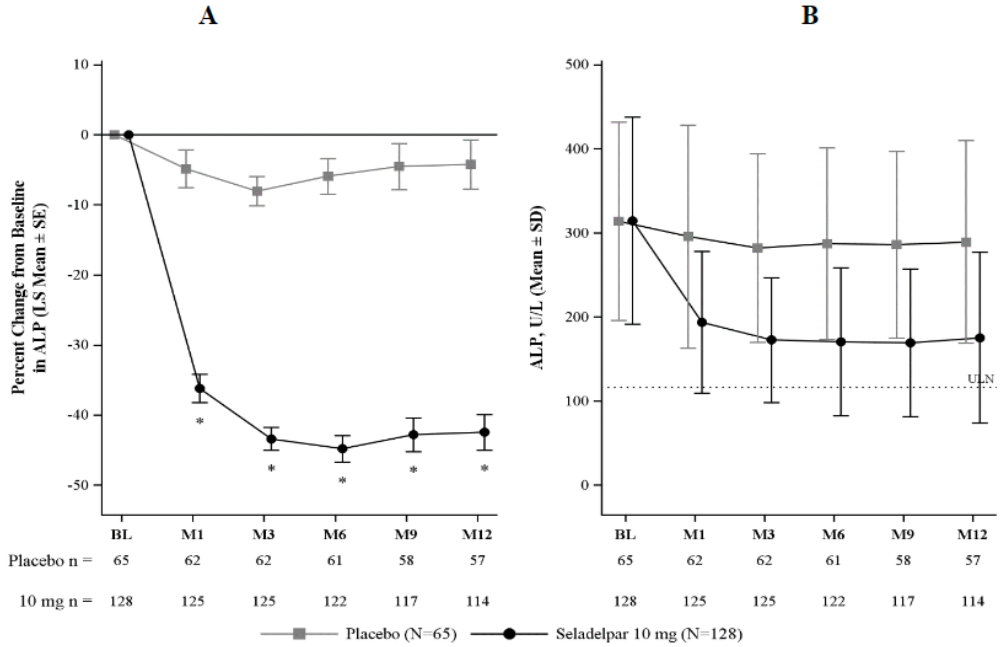
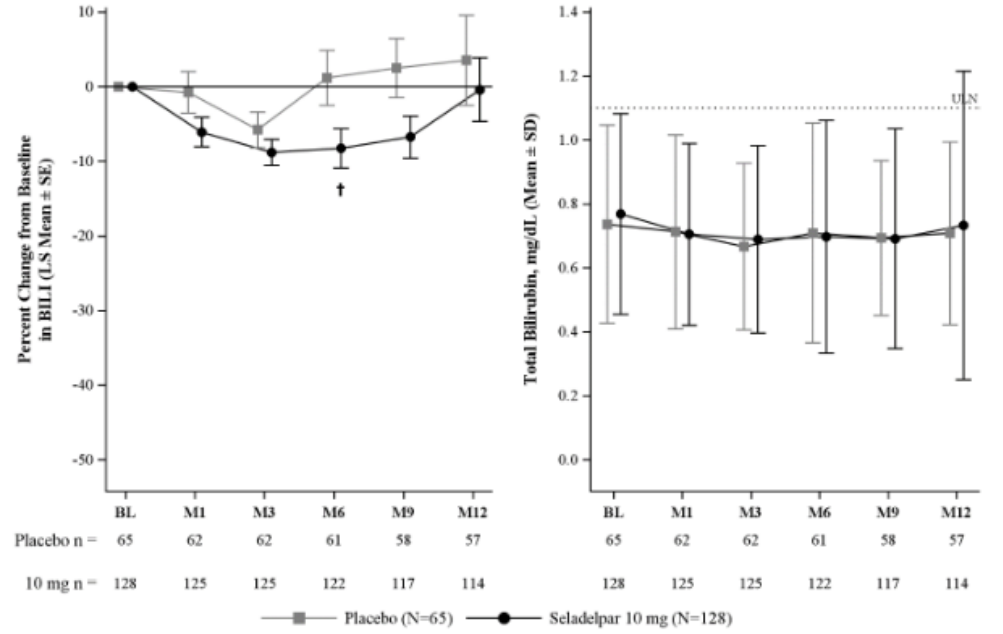


Figure 13: Percent change from baseline and mean values of total bilirubin over time (ITT analysis set)



Abbreviation: BILI = total bilirubin; BL = baseline; ITT = intent-to-treat; LS = least squares; M = Month; MMRM = mixed-effect model repeated measure; NRS = numerical rating scale; ULN = upper limit of normal
n = number of subjects who had both a baseline value and a value at that timepoint.
ULN for Total bilirubin = 1.1 mg/dL
Percent change from baseline was estimated by the MMRM model including terms for baseline ALP, stratification variables (baseline ALP level: < 350 U/L and ≥ 350 U/L; baseline Pruritus NRS: < 4 and ≥ 4), treatment arm, visit, and treatment-by-visit interaction. Unstructured covariance was applied for the repeated measure.
†p < 0.05 vs placebo
Source: Table 14.2.12.2

At baseline, mean GGT values were comparable between treatment arms (269.0 U/L in the seladelpar arm and 287.5 U/L in the placebo arm. LS mean percent changes from baseline in GGT levels at Month 12 were -39.1% in the seladelpar arm compared with -11.4% in the placebo arm.

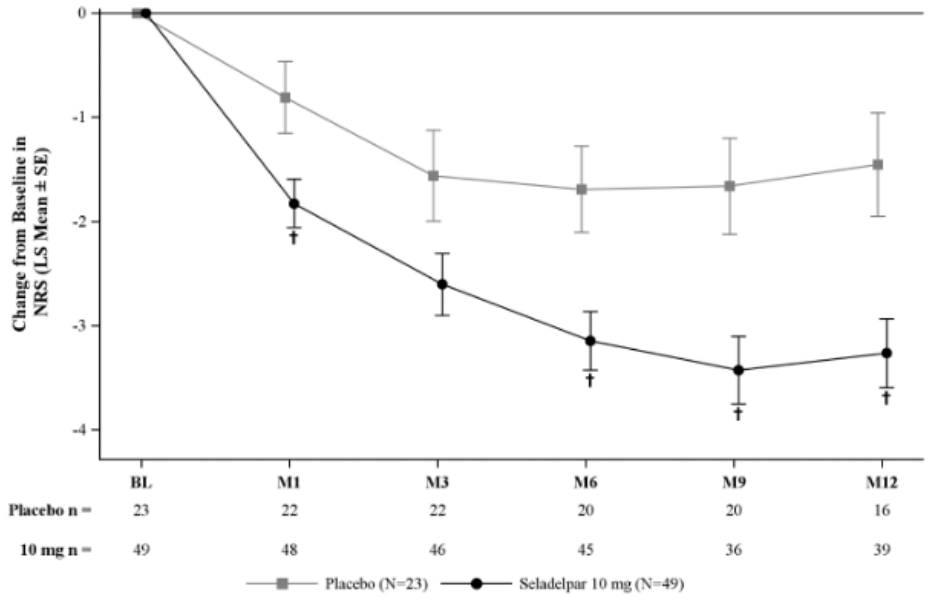
At baseline, mean ALT values were comparable between treatment arms (47.4 U/L in the seladelpar arm and 48.2 U/L in the placebo arm. Postbaseline reductions in ALT levels were greater in the seladelpar arm compared with the placebo arm starting at Month 3 and continuing through Month 12. LS mean percent changes from baseline in ALT levels at Month 12 were -23.5% in the seladelpar arm compared with -6.5% in the placebo arm.

Mean baseline AST values were comparable between treatment arms (39.6 U/L in the seladelpar arm and 41.7 U/L in the placebo arm). AST values were similar in both treatment arms over the course of the study and remained unchanged from baseline.

Mean baseline 5'-nucleotidase values were comparable between treatment arms (15.3 U/L in the seladelpar arm and 16.7 U/L in the placebo arm). Levels of 5'-nucleotidase decreased from baseline at Month 1 in subjects receiving seladelpar with further reductions at Months 3 through 12 (LS mean percent changes at Months 1, 3, 6, 9 and 12: -34.3%, -40.1%, -42.7%, -43.2%, -42.3%, respectively). Smaller decreases in 5'-nucleotidase levels were observed in subjects receiving placebo (LS mean percent changes at Months 1, 3, 6, 9 and 12: -10.5%, -12.0%, -14.1%, -17.8% and -20.8%, respectively).

Other endpoints regarding pruritus

Figure 14: Changes from baseline in pruritus NRS over time (MSPN analysis set)



Abbreviations: BL = baseline; M = month; LS = least squares; MMRM = mixed-effect model repeated measure; MSPN = moderate to severe Pruritus NRS; NRS = numerical rating scale
n = number of subjects who had both a baseline value and a value at that timepoint
Change from baseline was estimated by the MMRM model including terms for baseline NRS, stratification variables (baseline ALP level < 350 U/L vs ALP level ≥ 350 U/L), treatment arm, week, and treatment-by-week interaction. Unstructured structure is applied for the repeated measure and Kenward-Roger correction was applied for the denominator degrees of freedom.
† $p < 0.05$ vs placebo; at Month 3, p=0.0519
Source: Tables 14.2.9.2 and 14.2.5.1

Table 34: Analysis of pruritus NRS decrease of NRS ≥ 2, NRS ≥ 3, or NRS ≥ 4 (weekly averages) over time (MSPN analysis set)

	Placebo (N = 23)	Seladelpar 10 mg (N = 49)
Pruritus NRS Decrease ≥ 2 Response Rate[a,b]		
Month 1, n (%) (Wald 95% CI for Response Rate)	5 (21.7) (4.9, 38.6)	18 (36.7) (23.2, 50.2)
Month 3, n (%) (Wald 95% CI for Response Rate)	11 (47.8) (27.4, 68.2)	26 (53.1) (39.1, 67.0)
Month 6, n (%) (Wald 95% CI for Response Rate)	7 (30.4) (11.6, 49.2)	34 (69.4) (56.5, 82.3)
Month 9, n (%) (Wald 95% CI for Response Rate)	10 (43.5) (23.2, 63.7)	27 (55.1) (41.2, 69.0)
Month 12, n (%) (Wald 95% CI for Response Rate)	10 (43.5) (23.2, 63.7)	30 (61.2) (47.6, 74.9)
Pruritus NRS Decrease ≥ 3 Response Rate[b,c]		
Month 1, n (%) (Wald 95% CI for Response Rate)	1 (4.3) (0.0, 12.7)	12 (24.5) (12.4, 36.5)
Month 3, n (%) (Wald 95% CI for Response Rate)	4 (17.4) (1.9, 32.9)	17 (34.7) (21.4, 48.0)
Month 6, n (%) (Wald 95% CI for Response Rate)	5 (21.7) (4.9, 38.6)	22 (44.9) (31.0, 58.8)
Month 9, n (%) (Wald 95% CI for Response Rate)	7 (30.4) (11.6, 49.2)	21 (42.9) (29.0, 56.7)
Month 12, n (%) (Wald 95% CI for Response Rate)	5 (21.7) (4.9, 38.6)	23 (46.9) (33.0, 60.9)
Pruritus NRS Decrease ≥ 4 Response Rate[b,d]		
Month 1, n (%) (Wald 95% CI for Response Rate)	0 (0.0, 0.0)	5 (10.2) (1.7, 18.7)
Month 3, n (%) (Wald 95% CI for Response Rate)	2 (8.7) (0.0, 20.2)	11 (22.4) (10.8, 34.1)
Month 6, n (%) (Wald 95% CI for Response Rate)	4 (17.4) (1.9, 32.9)	14 (28.6) (15.9, 41.2)
Month 9, n (%) (Wald 95% CI for Response Rate)	2 (8.7) (0.0, 20.2)	15 (30.6) (17.7, 43.5)
Month 12, n (%) (Wald 95% CI for Response Rate)	2 (8.7) (0.0, 20.2)	15 (30.6) (17.7, 43.5)

PBC-40 QoL – Itch Domain

Mean scores of the Itch Domain of the PBC-QoL questionnaire at baseline were generally comparable between treatment arms (seladelpar: 8.7 vs placebo: 9.6). Consistent with the results from the analysis of the key secondary efficacy endpoint of changes in Pruritus NRS at Month 6, LS mean changes in the Itch Domain from baseline to Month 6 were -2.20 in the seladelpar arm vs -0.40 in the placebo arm.

Effect on the 5-D Itch Scale (MSPN Analysis Set)

The effect of seladelpar on the 5-D Itch scale in the MSPN Analysis Set was assessed as an exploratory endpoint. The total scores of the 5-D Itch scale at baseline were similar between treatment arms

(seladelpar: 16.2; placebo: 16.4). At Month 6, the LS mean change from baseline in the total score of the 5-D Itch scale was -4.7 in the seladelpar arm compared with -1.3 in the placebo arm.

Additional observations pertinent to the changes in distinct domains/items of the 5-D Itch Scale in the MSPN Analysis Set are described below:

• Distribution: At baseline, the distribution domain of the 5-D Itch score had similar mean scores between treatment arms (3.1 in both arms). At Month 6, the results were consistent with those of the key secondary endpoint in Pruritus NRS, showing greater decreases from baseline in the distribution domain of the 5-D Itch scale in the seladelpar arm compared with placebo (LS mean change -0.6 in seladelpar vs 0.2 in placebo).

• Degree: At baseline, the degree domain of the 5-D Itch score had similar scores between treatment arms (3.3 in both arms). At Month 6, greater decreases from baseline in the degree domain were observed in the seladelpar arm compared with placebo (LS mean change -0.9 in seladelpar vs -0.3 in placebo).

• Disability: At baseline, the disability domain of the 5-D Itch score had similar scores between treatment arms (3.5 in both arms). At Month 6, greater decreases from baseline in the disability domain were observed in the seladelpar arm compared with placebo (LS mean change -1.2 in seladelpar vs -0.2 in placebo).

• Sleep: At baseline, the sleep item of the 5-D Itch score had similar scores between treatment arms (3.2 in seladelpar vs 3.0 in placebo). At Month 6, greater decreases from baseline in the sleep item were observed in the seladelpar arm compared with those in placebo (LS mean change -1.0 in seladelpar vs -0.3 in placebo).

Pruritus in the overall population

Effect on Pruritus NRS Over Time (ITT Analysis Set)

Figure 15: MMRM analysis of weekly pruritus NRS change from baseline (ITT analysis set)

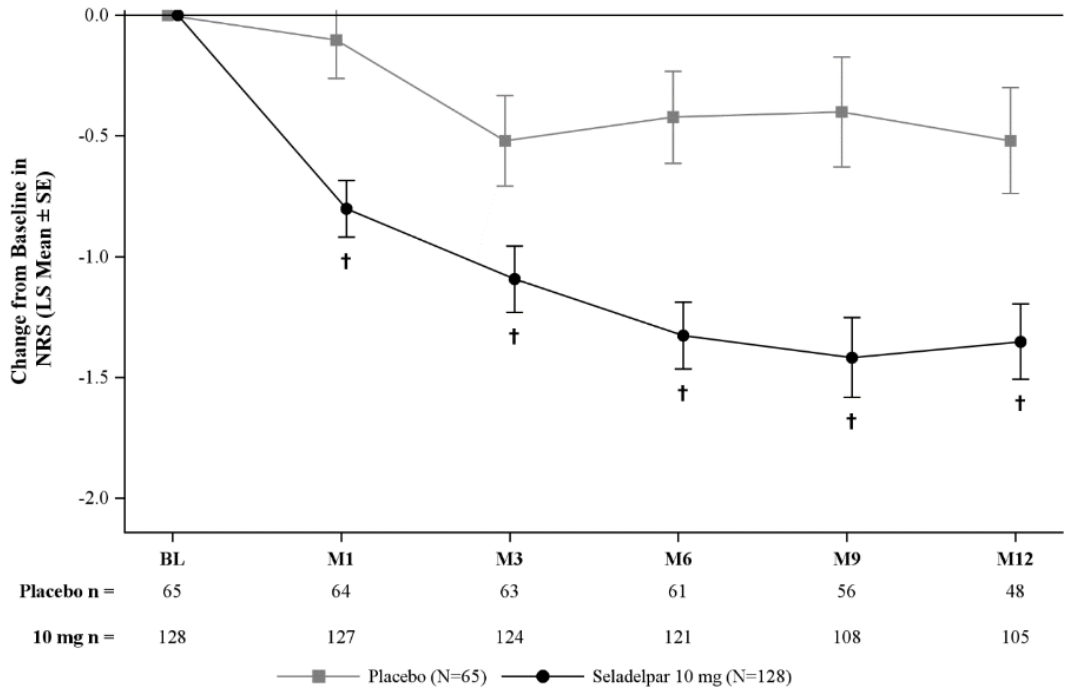


Table 35: The percentage of subjects with a decrease from baseline in pruritus NRS ≥ 4 or postbaseline pruritus NRS = 0 in subjects with baseline pruritus NRS > 0 (ITT subjects)

Subjects with Pruritus NRS=0 or Pruritus NRS Decrease >= 4, n/m (%)	Placebo (N=65)	Seladelpar 10 mg (N=128)
Month 1, n/m (%)	3/ 50 (6.0)	13/ 98 (13.3)
Wald 95% CI for Response Rate	(0.0, 12.6)	(6.5, 20.0)
Month 3, n/m (%)	8/ 50 (16.0)	23/ 98 (23.5)
Wald 95% CI for Response Rate	(5.8, 26.2)	(15.1, 31.9)
Month 6, n/m (%)	10/ 50 (20.0)	28/ 98 (28.6)
Wald 95% CI for Response Rate	(8.9, 31.1)	(19.6, 37.5)
Month 9, n/m (%)	9/ 50 (18.0)	29/ 98 (29.6)
Wald 95% CI for Response Rate	(7.4, 28.6)	(20.6, 38.6)
Month 12, n/m (%)	9/ 50 (18.0)	24/ 98 (24.5)
Wald 95% CI for Response Rate	(7.4, 28.6)	(16.0, 33.0)

Table 36: Analysis of the postbaseline pruritus NRS = 0 response rate for subjects with baseline NRS > 0 (weekly averages)

Subjects with Pruritus NRS=0, n/m (%)	Placebo (N=65)	Seladelpar 10 mg (N=128)
Month 1, n/m (%)	3/ 50 (6.0)	8/ 98 (8.2)
Wald 95% CI for Response Rate	(0.0, 12.6)	(2.7, 13.6)
Month 3, n/m (%)	6/ 50 (12.0)	12/ 98 (12.2)
Wald 95% CI for Response Rate	(3.0, 21.0)	(5.8, 18.7)
Month 6, n/m (%)	6/ 50 (12.0)	16/ 98 (16.3)
Wald 95% CI for Response Rate	(3.0, 21.0)	(9.0, 23.6)
Month 9, n/m (%)	7/ 50 (14.0)	19/ 98 (19.4)
Wald 95% CI for Response Rate	(4.4, 23.6)	(11.6, 27.2)
Month 12, n/m (%)	7/ 50 (14.0)	15/ 98 (15.3)
Wald 95% CI for Response Rate	(4.4, 23.6)	(8.2, 22.4)

Effect on PBC-40 Quality of Life (ITT Analysis Set)

Additional observations on the PBC-40 QoL questionnaire are summarised below for the ITT Analysis Set:

• Mean baseline total scores of the PBC-40 QoL questionnaire were similar between treatment arms (seladelpar: 91.6; placebo: 91.4) There were no meaningful between arm differences in the total scores of the PBC-40 QoL questionnaire over the course of the study.

• Pertinent to the sleep disturbance item of the PBC-40 QoL, at Month 6, a similar percentage of subjects in the seladelpar and placebo arms had improvements in sleep.

Changes in GLOBE and UK-PBC Risk Scores

The effects of seladelpar on the GLOBE and UK-PBC risk scores in the ITT Analysis Set were assessed as secondary endpoints. Overall, baseline values were similar across treatment arms for both the GLOBE and the UK-PBC risk scores. Analysis of GLOBE risk scores showed a greater decrease in the risk of clinical outcomes in the seladelpar arm compared with placebo at all study timepoints evaluated ($p < 0.0001$). Based on the GLOBE risk score, a greater decrease in the estimated risk of clinical outcomes was observed in the seladelpar arm compared with placebo, with a HR of 0.68 at Month 12. Seladelpar treatment was also associated with trends in decreased risk of clinical outcomes as evaluated by the 5-year, 10-year, and 15-year UK-PBC risk scores when compared with placebo (15-year UK-PBC risk score: $p < 0.05$ for all timepoints except Month 12). Based on the 15-year UK-PBC risk score, a greater decrease in the estimated risk of clinical outcomes was observed in the seladelpar arm compared with the placebo arm from Month 1 through Month 12, with a HR of 0.87 at Month 12.

Effect on PBC Clinical Outcomes

Time to first occurrence of a PBC clinical outcome event in the ITT Analysis Set was assessed as

a secondary endpoint. One subject in the seladelpar arm was positively adjudicated as having experienced PBC clinical outcome events. The subject on the seladelpar arm experienced hospitalisation due to variceal bleeding and worsening of liver cirrhosis due to decompensated PBC on Study Day 379.

Effect on PBC Response Criteria

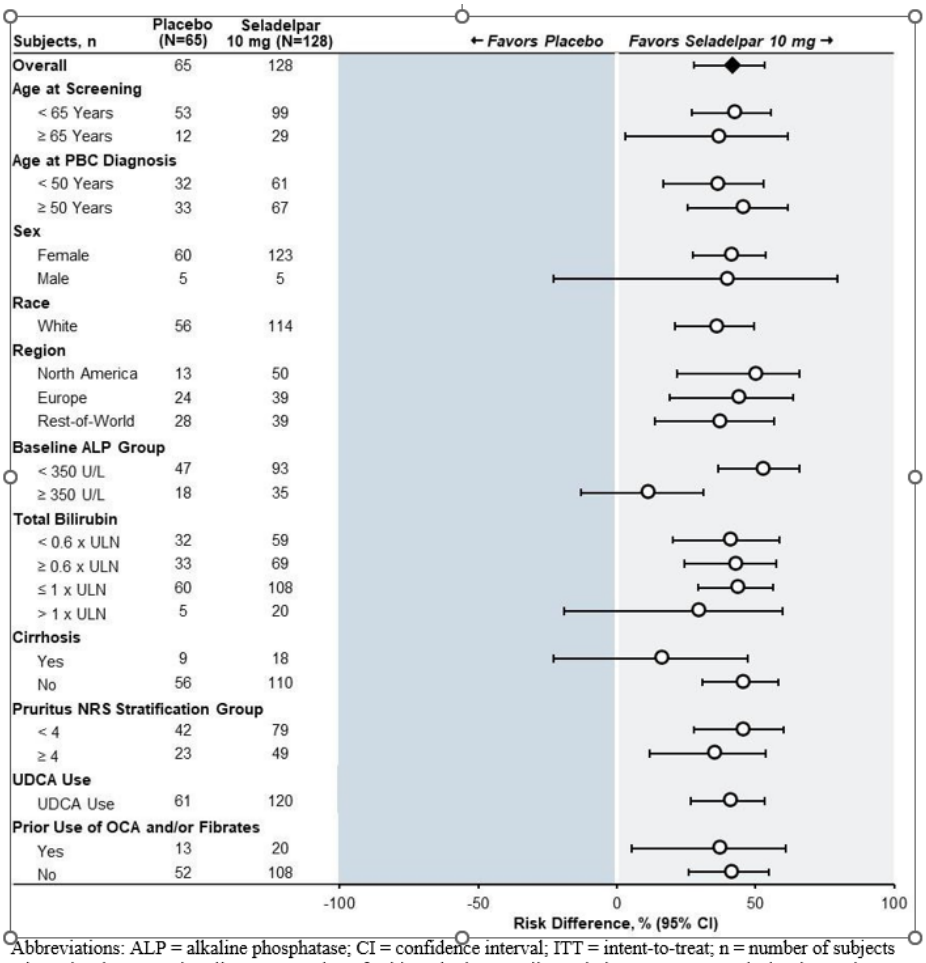
Assessments of treatment response in the ITT Analysis Set according to the published criteria for PBC (Barcelona, Paris I, Paris II, Toronto I, Toronto II, and Rotterdam) were exploratory endpoints of the study.

The percentage of subjects achieving the Barcelona (6.2% vs 58.6%), Paris I (55.4% vs 69.5%), Paris II (12.3% vs 50%), Toronto I (26.2% vs 65.6%), and Toronto II (27.7% vs 67.2%) PBC response criteria was higher in the seladelpar arm compared with the placebo arm at month 12. The difference in the percentage of subjects achieving the Rotterdam PBC response criteria was difficult to interpret due to small sample sizes.

- **Ancillary analyses**

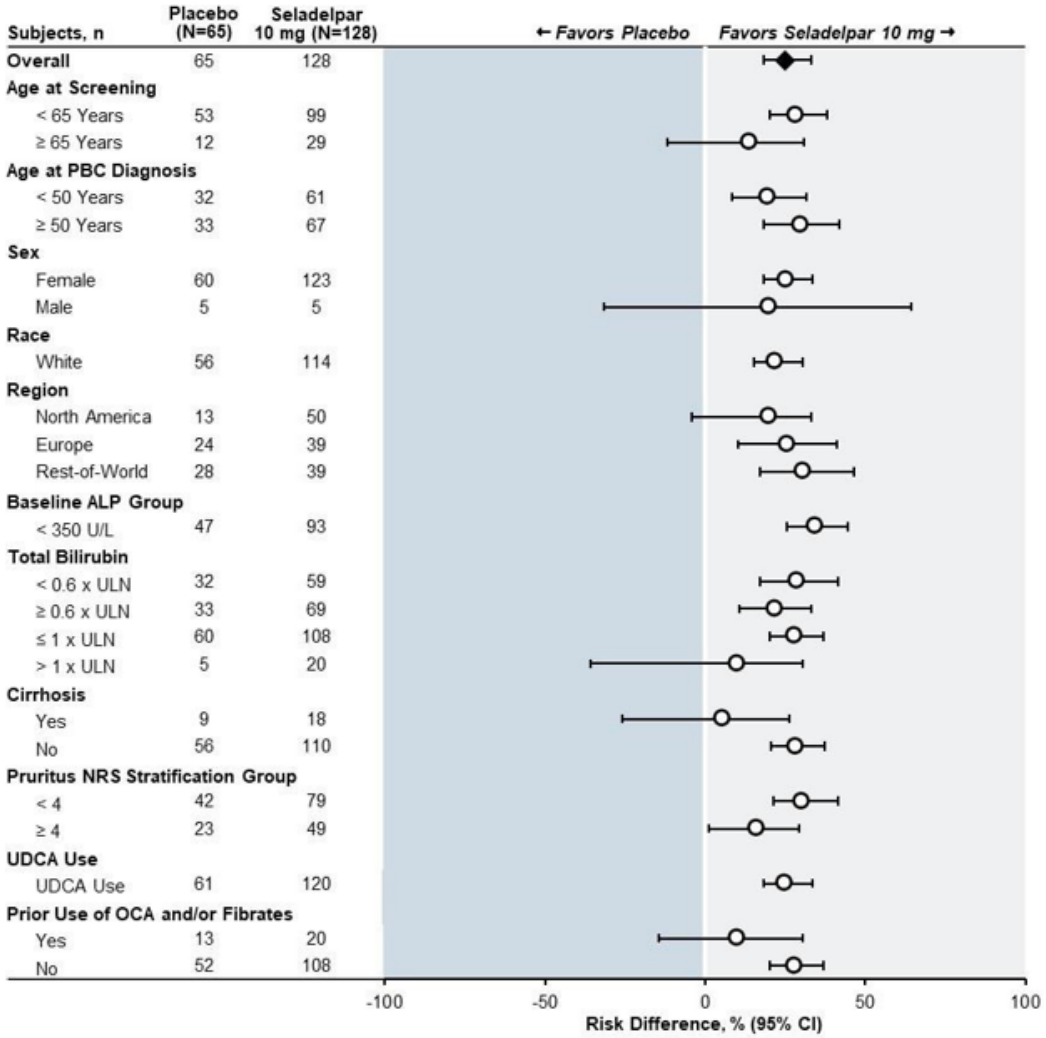
The effects observed with seladelpar on prespecified subgroups on the primary efficacy endpoint and key secondary endpoints are presented below.

Figure 16: Study CB8025-32048: Forest plot of the composite endpoint response rate at month 12 by subgroup (ITT analysis set)



Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; ITT = intent-to-treat; n = number of subjects in each subgroup at baseline; N = number of subjects in the overall population; NRS = numerical rating scale;

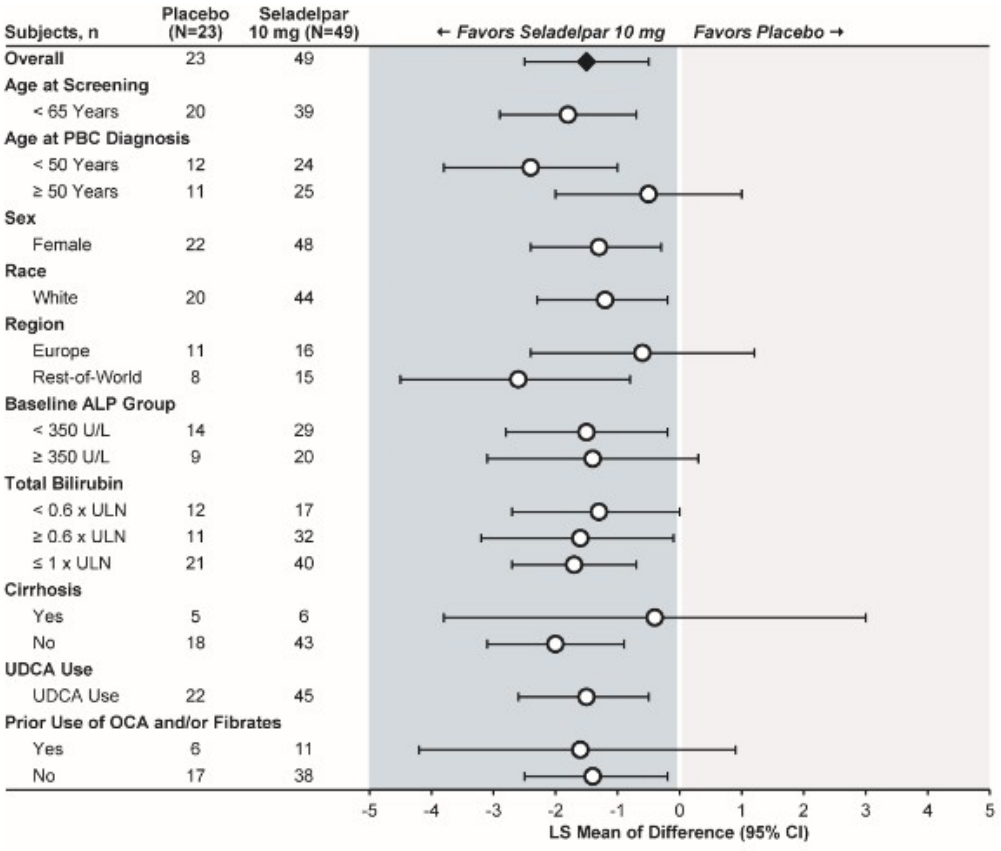
Figure 17: Study CB8025-32048: forest plot of the response rates of ALP normalisation at month 12 by subgroup



Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; ITT = intent-to-treat; n = number of subjects in each subgroup at baseline; N = number of subjects in the overall population; NRS = numerical rating scale; OCA = obeticholic acid; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

Normalisation of ALP defined as ALP ≤ ULN. Subgroup analyses were not performed when group size was < 5 subjects.

Figure 18: Study CB8025-32048: Forest plot of changes in weekly averaged pruritus NRS at month 6 by subgroup (MSPN analysis set)



Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; ITT = intent-to-treat; LS = least squares; n = number of subjects in each subgroup at baseline; N = number of subjects in the overall population; NRS = numerical rating scale; MSPN = moderate to severe Pruritus NRS; OCA = obeticholic acid; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

Subgroups were not presented when groups sizes were < 5 subjects (including some race subgroups and subjects intolerant to UDCA). Overall, the effects observed with seladelpar on the primary efficacy endpoint and key secondary efficacy endpoints were observed across evaluable subgroups, with some overlap in risk difference CIs between the overall population and individual subgroups as well as between subgroup pairs. In the subgroup of subjects with baseline ALP ≥ 350 U/L, the proportion of responders for the primary composite biochemical endpoint in the seladelpar arm was lower compared with that in subjects with baseline ALP < 350 U/L, and there were no subjects with baseline ALP ≥ 350 who achieved normalisation of ALP in either treatment arm. As the applicant pointed out, this was not unexpected given that requirements to achieve ALP < 1.67× ULN or < 1× ULN were greater for subjects with higher ALP levels at baseline.

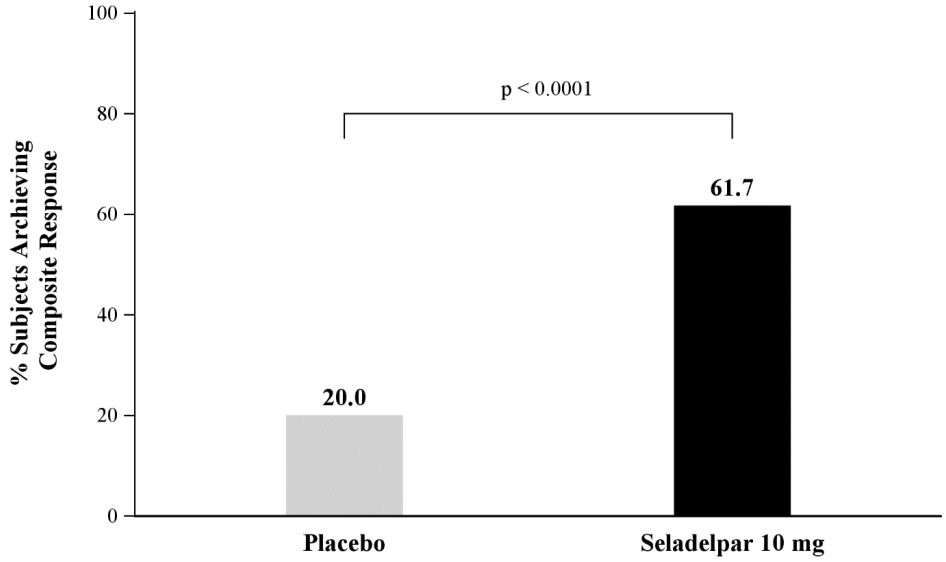
Some additional information regarding the subgroups with monotherapy and cirrhosis patients are provided in the section *Analysis performed across trials (pooled analyses and meta-analysis*) further below.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37: Summary of efficacy for trial CB8025-32048 (RESPONSE)

Title	RESPONSE: A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)	
Study Identifier	CB8025-32048 EudraCT Number: 2020-004348-27	
Design	Phase 3, international, multicentre study using a randomised, double-blind, placebo controlled, parallel-arm design where study drug (seladelpar or placebo) was administered daily for up to 12 months as an oral capsule in PBC subjects.	
	Duration of main phase:	12 Months
	Duration of Run-in phase:	Up to 2 weeks
	Duration of Extension phase:	N/A
Hypothesis	This pivotal, international, double-blind, placebo-controlled study included 193 subjects randomised in a 2:1 ratio to receive seladelpar or placebo across 90 sites in 24 countries. The ITT Analysis Set was used for efficacy analyses with the exception of secondary endpoints evaluated in subjects with moderate to severe pruritus, defined as baseline Pruritus NRS ≥ 4.	
Treatment Groups	Seladelpar arm: Oral seladelpar 10 mg capsule once daily (qd)	128 subjects were randomised to the seladelpar arm
	Placebo arm: Oral seladelpar-matched placebo (qd)	65 subjects were randomised to the placebo arm
Endpoints and Definitions	**Primary Endpoint**	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 Terminology Criteria for Adverse Events [CTCAE] Version 5.0), biochemistry and haematology
	Key Secondary Endpoint	1. Proportion of subjects with ALP ≤ 1.0× ULN at 12 months (e.g., normalisation) 2. Change from baseline in weekly averaged Pruritus NRS in subjects with baseline NRS ≥ 4 at 6 months
Database Lock	30 Aug 2023	
Results and Analysis		
Analysis Description	**Primary Analysis**	

Analysis population and time point description	Intent-To-Treat (ITT) Analysis Set: Any subject who was randomised into the study and received at least 1 dose of study drug. The ITT Analysis Set was the primary analysis set used for efficacy analyses with the exception of secondary endpoints evaluated for subjects with moderate to severe pruritus. Subjects were analysed according to randomised treatment assignment. Per-protocol (PP) Analysis Set: Any subject who was in the ITT Analysis Set and had at least 1 postbaseline ALP and total bilirubin evaluation without any protocol violation that was deemed to impact the efficacy analysis.
Descriptive statistics and estimate variability	The primary efficacy endpoint of the proportion of subjects achieving the composite biochemical response evaluated at Month 12 was analysed using Cochran-Mantel-Haenszel (CMH) test adjusted for both randomisation stratification variables (ALP level: < 350 U/L and ≥ 350 U/L; Pruritus NRS: < 4 and ≥ 4) in the ITT Analysis Set. Control of study-wide Type I error was maintained at 5% using a hierarchical fixed-sequence methodology for the primary and key secondary efficacy analyses as defined in the SAP.
Effect estimate per comparison	 Abbreviations: ALP = alkaline phosphatase; 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 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. Subjects with missing data at the specified timepoint for response evaluation were considered non-responders. Two-sided p-value for pair-wise comparison was based on the CMH test adjusted for both randomisation 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.

Effect estimate per comparison

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 non-responders.

[c] Two-sided p-value for pair-wise comparison was based on the CMH test adjusted for both randomisation 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.

Effect estimate per comparison

Sensitivity Analysis of Composite Biochemical Response at Month 12 (Complete Case and Treatment Policy Strategy) (ITT Analysis Set)

	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	Risk Difference (Miettinen-Nurminen 95% CI)	CMH test p-value[b]
	Composite Endpoint Response Rate[a] n (%)			
Complete Case Analysis[c], n/m (%)	13 / 57 (22.8)	79 / 114 (69.3)	46.5 (31.4, 58.9)	p < 0.0001
Treatment Policy Strategy Analysis[d], n/N (%)	13 / 65 (20.0)	80[e] / 128 (62.5)	42.5 (28.5, 54.2)	p < 0.0001

Abbreviations: ALP = alkaline phosphatase; CMH = Cochran-Mantel-Haenszel; ITT= intent-to-treat; NRS = numerical rating scale; ULN = upper limit of normal
N = total number of subjects, n/m (%) = (number of responders/number of subjects who have assessment at Month 12) x 100%

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

[b] Two-sided p-value for pair-wise comparison was based on the CMH test adjusted for both randomisation 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.

[c] Subjects with missing data at Month 12 were excluded from analysis.

[d] Data collected following treatment discontinuation were included in data summaries or inferential analyses.

[e] Subject [redacted] had laboratory assessments 27 days after last treatment date and was classified as a responder.

Effect estimate per comparison

Sensitivity Analysis of Composite Biochemical Response at Month 12 (Control-based Multiple Imputation) (ITT Analysis Set)

Control-based Multiple Imputation[a]	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	CMH test p-value[b]
Observed Cases, n (%)	57 (87.7)	114 (89.1)	p < 0.0001
Subjects Requiring Imputation, n (%)[a]	8 (12.3)	14 (10.9)	

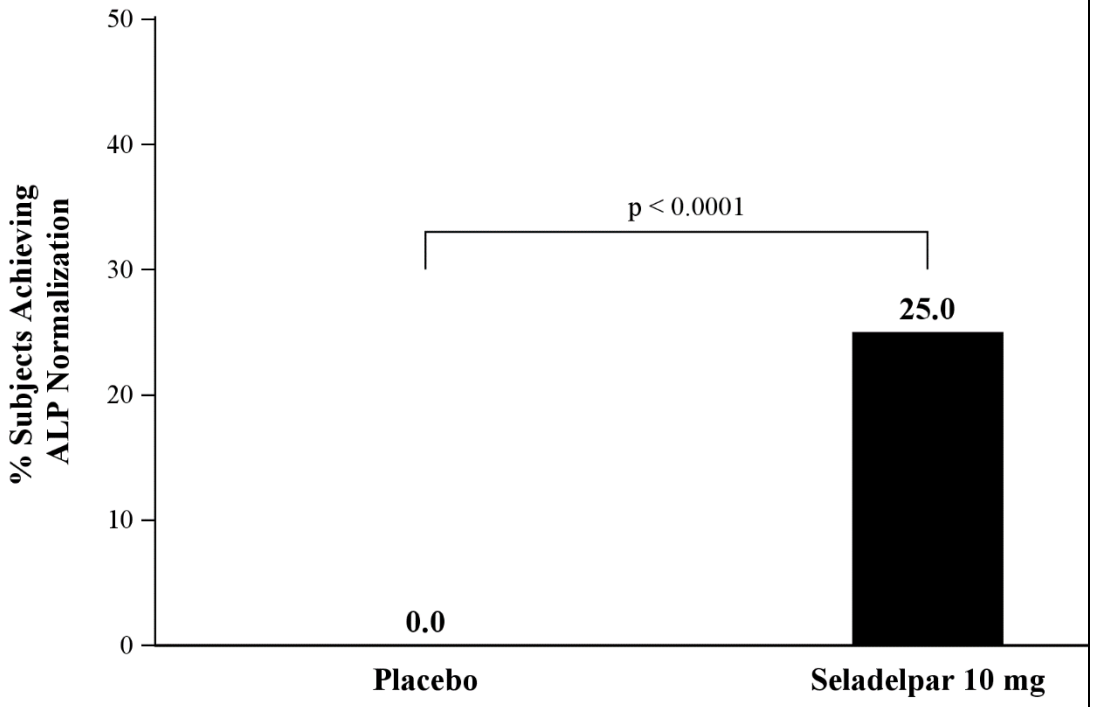
Abbreviation: ALP = alkaline phosphatase; CMH = Cochran-Mantel-Haenszel; ITT= intent-to-treat
N = total number of subjects. n = number of subjects in the category

[a] Missing ALP and total bilirubin results at Month 12 were imputed with a control-based multiple imputation method and then used to classify a subject as a responder or a nonresponder.

[b] Two-sided p-value for pair-wise comparison was based on combining the CMH test results out of 100 multiple imputed datasets.

Notes	The study met the primary efficacy endpoint of the composite biochemical response of ALP < 1.67× ULN, ≥ 15% reduction in ALP, and total bilirubin ≤ 1.0 ULN at Month 12. A significantly higher percentage of subjects receiving seladelpar (61.7%; 79/128) achieved the primary efficacy endpoint compared with placebo (20.0%; 13/65) ($p < 0.0001$). At Month 12, 65.6% of subjects in the seladelpar arm compared with 26.2% in the placebo arm achieved the ALP < 1.67× ULN component of the composite biochemical response endpoint. In addition, a higher percentage of subjects receiving seladelpar (83.6%) experienced a decrease from baseline of ≥ 15% in ALP levels, compared with subjects who received placebo (32.3%). The percentage of subjects with total bilirubin ≤ 1.0× ULN was 81.3% and 76.9% in the seladelpar and placebo arms, respectively. Higher percentages of responders in the seladelpar arm compared with placebo were observed as early as Month 1, and these differences were maintained with ongoing treatment throughout the course of the study. Results from multiple prespecified sensitivity analyses, including complete case and treatment policy strategy analyses, and control-based multiple imputation analysis of the primary and the two key secondary efficacy endpoints validated the robustness of the primary analyses of the corresponding efficacy endpoints. Results from the Tipping Point analyses also showed that even in the unlikely case wherein all subjects in the placebo arm with missing data at Month 12 were categorised as responders for the primary efficacy endpoint and the key secondary efficacy endpoint of ALP normalisation, the seladelpar arm would still perform significantly better compared with the placebo arm. Results from the analysis of prespecified subgroups are as follows: • Consistent with the analyses in the ITT Analysis Set, analyses of prespecified subgroups revealed higher percentages of responders for subjects in the seladelpar arm compared with placebo for the composite biochemical response endpoint at Month 12 across evaluable subgroups. ○ Analyses of the primary efficacy biochemical response endpoint for subgroups including female vs male, age at Screening ≥ 65 years vs < 65 years, age at PBC diagnosis < 50 years vs ≥ 50 years, North America subjects vs Europe vs Rest of the world, prior use of OCA/fibrates vs no prior use, total bilirubin < 0.6× ULN vs ≥ 0.6× ULN, Pruritus NRS < 4 vs ≥ 4, cirrhosis vs no cirrhosis, and total bilirubin ≤ 1× ULN vs > 1× ULN at baseline demonstrated a generally similar treatment effect with seladelpar across subgroups. ○ A higher percentage of subjects with ALP ≥ 350 U/L at baseline in the seladelpar arm reached the primary efficacy endpoint (22.9%), compared with the placebo group (11.1%); however, the proportion of responders in the seladelpar arm was lower compared with that in the overall ITT Analysis Set and with subjects with ALP < 350 U/L at baseline, consistent with higher baseline ALP requiring greater reductions to achieve the ALP < 1.67× ULN component of the composite biochemical response endpoint. ○ Despite small group sizes, a higher percentage of subjects who received seladelpar as monotherapy achieved the primary efficacy endpoint compared with those who received placebo.
Analysis Description	Key Secondary Analysis

Descriptive statistics and estimate variability	Intent-To-Treat (ITT) Analysis Set: Any subject who was randomised into the study and received at least 1 dose of study drug. The ITT Analysis Set was the primary analysis set used for efficacy analyses with the exception of secondary endpoints evaluated for subjects with moderate to severe pruritus. Subjects were analysed according to randomised treatment assignment. Moderate to Severe Pruritus NRS (MSPN) Analysis Set: Subjects in the ITT Analysis Set who had a baseline NRS value ≥ 4. The MSPN Analysis Set was the primary analysis set for secondary endpoints based on NRS evaluations. Subjects were analysed according to randomised treatment assignment. Per-protocol (PP) Analysis Set: Any subject who was in the ITT Analysis Set and had at least 1 postbaseline ALP and total bilirubin evaluation without any protocol violation that was deemed to impact the efficacy analysis.
	The key secondary efficacy endpoint of the proportion of subjects who achieved normalisation of ALP levels at Month 12 was analysed in the ITT Analysis Set using the same approach as described for the primary efficacy endpoint analysis. Change from baseline in weekly averaged Pruritus NRS at 6 months, the other key secondary endpoint, was analysed using a mixed-effect model for repeated measures (MMRM) for subjects in the MSPN Analysis Set. The model included terms for baseline NRS, randomisation stratum (ALP level < 350 U/L vs ≥ 350 U/L), treatment group, week, and treatment-by-week interaction. Control of study-wide Type I error was maintained at 5% using a hierarchical fixed-sequence methodology for the primary and key secondary efficacy analyses as defined in the SAP.

Effect estimate per comparison	Percentage of Subjects Who Achieved ALP Normalisation at Month 12 (ITT Analysis Set)  n/N = 0/65 32/128 Abbreviations: ALP = alkaline phosphatase; 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 subject was designated as a responder (achieving normalisation) if the ALP value at Month 12 was ≤ 1.0 × ULN. Subjects with missing data at the specified timepoint for response evaluation were considered as non-responders. Two-sided p-value for pair-wise comparison was based on the Cochran-Mantel-Haenszel test adjusted for both randomisation 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.

Effect estimate per comparison

Analysis of the Normalisation of ALP Response Rate at Month 12 (ITT Analysis Set)

	Placebo (N = 65)	**Seladelpar 10 mg (N = 128)**
Subjects with ALP ≤ 1.0× ULN at Month 12[a,b], n (%) (Wald 95% CI for Response Rate)	0 (0.0, 0.0)	32 (25.0) (17.5, 32.5)
Risk Difference (Miettinen-Nurminen 95% CI)		25.0 (18.3, 33.2)
CMH test p-value[c]		p < 0.0001
Mantel-Fleiss Criterion[c]		10.8
Breslow-Day p-value[c]		NE

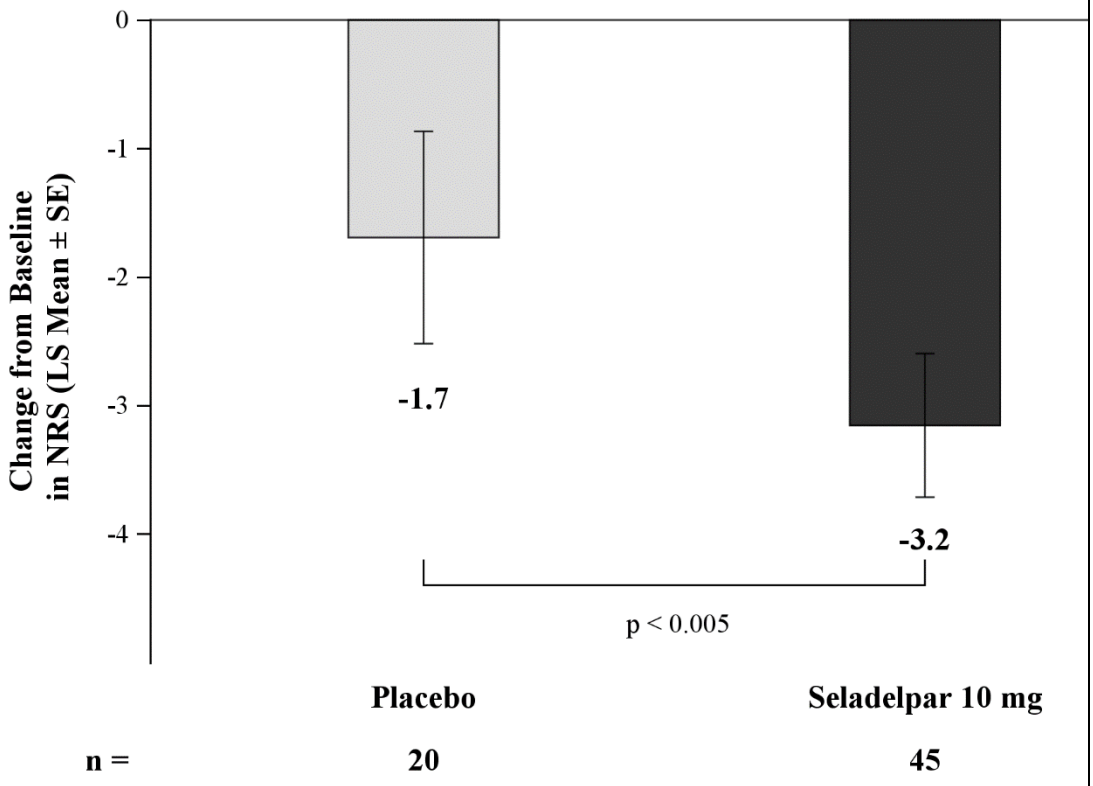
Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT= intent-to-treat; NE = not estimable; ULN = upper limit of normal

N = total number of subjects, n = number of subjects in the category

a A subject was designated as a responder if the ALP value at Month 12 was ≤ 1.0 × ULN.

b Subjects with missing data at the specified timepoint for response evaluation were considered as non-responders.

c Two-sided p-value for pair-wise comparison was based on the Cochran-Mantel-Haenszel test adjusted for both randomisation 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.

Effect estimate per comparison	Effect on Weekly Averages of Pruritus NRS at Month 6 in Subjects with Baseline NRS ≥ 4 (MSPN Analysis Set)  Abbreviations: ALP = alkaline phosphatase; LS = least squares; MMRM = mixed-effect model repeated measure; MSPN = moderate to severe Pruritus NRS; NRS = numerical rating scale N = total number of subjects, n = number of subjects with non-missing or imputed results at specific timepoint Baseline Pruritus NRS was defined as the mean of all daily recorded scores during the Run-in Period and on Day 1. A missing assessment at a specific timepoint was imputed as an average of the two adjacent weekly averages (at most one week apart): if only one adjacent weekly average was available, it was imputed by the available adjacent weekly average; if no adjacent weekly average was available, it was not imputed. Change from baseline was estimated by the MMRM model including terms for baseline Pruritus NRS, stratification variable (baseline ALP level < 350 U/L vs ALP level ≥ 350 U/L), treatment arm, week, and treatment-by-week interaction. Unstructured covariance was applied for the repeated measure, and Kenward-Roger correction was applied for the denominator degrees of freedom.

Effect estimate per comparison

MMRM Analysis of Changes from Baseline at Month 6 in Weekly Averaged Pruritus NRS (MSPN Analysis Set)

Visit	Placebo (N = 23)	Seladelpar 10 mg (N = 49)
Baseline		
n	23	49
Mean (SD)	6.6 (1.44)	6.1 (1.42)
Median	7.1	5.9
Q1, Q3	5.6, 7.7	4.9, 7.4
Min, Max	4, 9	4, 9
Month 6 Change from Baseline[a]		
n	20	45
Mean (SD)	-1.9 (1.96)	-3.1 (2.07)
Median	-1.9	-2.9
Q1, Q3	-3.3, -0.4	-4.4, -2.0
Min, Max	-6, 1	-8, 2
LS Mean (SE)[b]	-1.7 (0.41)	-3.2 (0.28)
LS Mean of Difference (95% CI)		-1.5 (-2.5, -0.5)
p-value		p=0.0047

Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; LS = least squares; MMRM = mixed-effect model repeated measure; MSPN = moderate to severe Pruritus NRS; NRS = numerical rating scale

N = total number of subjects, n = number of subjects with non-missing or imputed results at specific timepoint

Baseline Pruritus NRS was defined as the mean of all daily recorded scores during the Run-in Period and on Day 1.

a A missing assessment at a specific timepoint was imputed as an average of the two adjacent weekly averages (at most one week apart): if only one adjacent weekly average was available, it was imputed by the available adjacent weekly average; if no adjacent weekly average was available, it was not imputed.

b Change from baseline was estimated by the MMRM model including terms for baseline Pruritus NRS, randomisation stratum (baseline ALP level < 350 U/L vs ALP level ≥ 350 U/L), treatment arm, week, and treatment-by-week interaction. Unstructured covariance was applied for the repeated measure, and Kenward-Roger correction was applied for the denominator degrees of freedom.

Effect estimate per comparison

Sensitivity Analysis of Normalisation of ALP at Month 12 (Complete Case and Treatment Policy Strategy) (ITT Analysis Set)

	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	Risk Difference (Miettinen-Nurminen 95% CI)	p-value[b]
	ALP Normalisation Response Rate[a] n (%)			
Complete Case Analysis[c], n/m (%)	0/57 (0)	32/114 (28.1)	28.1 (20.6, 37.0)	p < 0.0001
Treatment Policy Strategy Analysis[d], n/m (%)	0	34/128[e] (26.6)	26.6 (19.7, 34.8)	p < 0.0001

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/m (%) = (number of responders/number of subjects who had assessment at Month 12) × 100%.

a A subject was designated a responder if the following condition was met: ALP ≤ 1.0× ULN.

b Two-sided p-value for pair-wise comparison was based on the CMH test adjusted for both randomisation 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. Mantel-Fleiss criterion was used to assess the validity of the chi-square approximation for the distribution of the Mantel-Haenszel statistic.

c Subjects with missing data at Month 12 were excluded from analysis.

d Data collected following treatment discontinuation were included in data summaries or inferential analyses.

e Subject had an ALP assessment 27 days after last treatment date and was classified as a responder; subject had an ALP assessment 15 days after last treatment date and was classified as a responder.

Effect estimate per comparison

Sensitivity Analysis of Normalisation of ALP at Month 12 (Control-based Multiple Imputation) (ITT Analysis Set)

Control-based Multiple Imputation[a]	Placebo (N = 65)	Seladelpar 10 mg (N = 128)	CMH test p-value[b]
Observed Cases, n (%)	57 (87.7)	114 (89.1)	p < 0.0001
Subjects Requiring Imputation, n (%)[a]	8 (12.3)	14 (10.9)	

Abbreviations: ALP = alkaline phosphatase; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat

N = total number of subjects, n = number of subjects in the category

a A missing ALP assessment at Month 12 was imputed with a control-based multiple imputation method and then used to classify a subject as a responder or a nonresponder.

b Two-sided p-value for pair-wise comparison was based on combining the CMH test results out of 100 multiple imputed datasets.

Sensitivity Analysis of Changes in Pruritus NRS from Baseline at Month 6 in Subjects with Pruritus NRS ≥ 4 (Complete Case and Treatment Policy Strategy Analyses) (MSPN Analysis Set)

	Placebo	Seladelpar 10 mg	LS Mean of Difference (95% CI)	p-value
	LS Mean Month-6 Changes from Baseline in Pruritus NRS[a] (SE)			
Complete Case Analysis[b] (placebo n = 20; seladelpar n = 43)	-1.8 (0.43)	-3.1 (0.29)	-1.4 (-2.4, -0.3)	0.0103
Treatment Policy Strategy Analysis[c,d] (placebo n = 20; seladelpar n = 46)	-1.7 (0.42)	-3.1 (0.28)	-1.4 (-2.4, -0.3)	0.0095

Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; LS = least squares; MSPN = moderate to severe Pruritus NRS; NRS = numerical rating scale
n = number of subjects included in the analysis in each arm
[a] Change from baseline was estimated by the MMRM model including terms for baseline NRS, stratification variable (baseline ALP level < 350 U/L vs ALP level ≥ 350 U/L), treatment arm, week, and treatment-by-week interaction. Unstructured covariance was applied for the repeated measure, and Kenward-Roger correction was applied for the denominator degrees of freedom.
[b] No data were imputed for complete case analyses, ie, missing records were excluded.
[c] A missing assessment at a specific timepoint was imputed as an average of the two adjacent weekly averages (at most one week apart): if only one adjacent weekly average was available, it was imputed by the available adjacent weekly average; if no adjacent weekly average was available, it was not imputed.
[d] Data collected following treatment discontinuation were included in data summaries or inferential analyses.

Effect estimate per comparison

Sensitivity Analysis of Changes in Pruritus NRS from Baseline at Month 6 in Subjects with Pruritus NRS ≥ 4 (Control-based Multiple Imputation) (MSPN Analysis Set)

Control-based Multiple Imputation[a]	Placebo (N = 23)	Seladelpar 10 mg (N = 49)	LS Mean of Difference[b] (95% CI)	p-value
Observed cases, n (%)	20 (87.0)	45 (91.8)	-1.3 (-2.4, -0.3)	0.0091
Subjects Requiring Imputation, n (%)[a]	3 (13.0)	4 (8.2)		

Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed-effect model repeated measure; MSPN = moderate to severe Pruritus NRS; NRS = numerical rating scale
N = total number of subjects, n = number of subjects in the category
[a] Missing assessments were imputed with a control-based multiple imputation method.
[b] Reported statistics were based on combining the MMRM results out of 100 multiple imputed datasets.

Effect estimate per comparison

MMRM Analysis of Changes in Monthly Observed Averages of Pruritus NRS from Baseline to Month 6 (MSPN Analysis Set)

Visit	**Placebo (N = 23)**	**Seladelpar 10 mg (N = 49)**
Baseline		
n	23	49
Mean (SD)	6.6 (1.44)	6.1 (1.42)
Median	7.1	5.9
Q1, Q3	5.6, 7.7	4.9, 7.4
Min, Max	4, 9	4, 9
Month 6 Change from Baseline[a]		
n	20	45
Mean (SD)	-1.8 (1.83)	-3.0 (2.01)
Median	-1.8	-2.9
Q1, Q3	-3.3, -0.5	-4.4, -1.9
Min, Max	-5, 1	-8, 1
LS Mean (SE)[b]	-1.7 (0.41)	-3.0 (0.27)
LS Mean of Difference (95% CI)		-1.3 (-2.2, -0.3)
p-value		0.0124

Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; LS= least squares; MMRM = mixed-effect model repeated measure; MSPN = moderate to severe Pruritus NRS; NRS = numerical rating scale

N = total number of subjects, n = number of subjects with non-missing or imputed results at specific timepoint

Baseline Pruritus NRS was defined as the mean of all daily recorded scores during the Run-in Period and on Day 1.

a A missing assessment at a specific timepoint was imputed as an average of the two adjacent monthly averages (at most one month apart); if only one adjacent monthly average was available, it was imputed by the available adjacent monthly average; if no adjacent monthly average was available, it was not imputed. Data collected after Month 6 were not used for imputation.

b Change from baseline was estimated by the MMRM model including terms for baseline NRS, stratification variable (baseline ALP level <350 U/L vs ALP level ≥ 350 U/L), treatment arm, week, and treatment-by-week interaction. Unstructured

	covariance was applied for the repeated measure, and Kenward-Roger correction was applied for the denominator degrees of freedom.

	The study also met the key secondary efficacy endpoint of ALP normalisation (ALP ≤ 1.0× ULN) at Month 12. A significantly higher percentage of subjects in the seladelpar arm (25%) achieved ALP normalisation compared with the placebo arm (0%) ($p < 0.0001$). Higher percentages of responders in the seladelpar arm compared with placebo were observed at Month 1 and these effects were maintained with ongoing treatment throughout the course of the study. The other key secondary endpoint of change in Pruritus NRS at Month 6 in subjects with moderate to severe pruritus at baseline (Pruritus NRS ≥ 4) was also met. Seladelpar treatment led to a statistically significant improvement in Pruritus NRS compared with placebo with an LS mean change of 3.2 vs 1.7, respectively ($p=0.0047$). 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. In addition, the percentage of subjects with a decrease in Pruritus NRS ≥ 2, NRS ≥ 3, and NRS ≥ 4 in the seladelpar arm was higher compared with the placebo arm across all study timepoints. In the ITT Analysis Set, in which all subjects were evaluated regardless of baseline Pruritus NRS, subjects in the seladelpar arm also experienced greater decreases in Pruritus NRS compared with those receiving placebo, with reductions in the seladelpar arm vs placebo observed at all study timepoints. The LS mean change from baseline at Month 6 in the ITT Analysis Set was 1.3 for the seladelpar arm, relative to 0.4 in placebo ($p=0.0001$). Sensitivity analyses, including complete case and treatment policy strategy analyses and a control-based multiple imputation analysis, were also performed to evaluate the robustness of the primary analyses of the key secondary efficacy endpoint of ALP normalisation at Month 12. Overall, the results from the sensitivity analyses by stratum were consistent with those of the primary analysis of this key secondary efficacy endpoint. None of the subjects with ALP ≥ 350 U/L, irrespective of Pruritus NRS (strata 3 and 4), achieved ALP normalisation in either treatment arm.
Notes	A similar percentage of subjects in both treatment arms required imputation for the control-based multiple imputation sensitivity analysis (10.9% seladelpar and 12.3% placebo). The results from this sensitivity analysis of the key secondary efficacy endpoint of ALP normalisation at Month 12 were consistent with those of the primary analyses for the corresponding secondary endpoint. A tipping point analysis was performed to explore the effect of missing data on the reliability of the primary analysis by determining the extent of missing data that would need to change for the analysis to tip from statistically significant to statistically insignificant. The number of subjects in each treatment arm with missing data that were categorised as non-responders was incrementally decreased by 1 (and thus increasing the count of responders) to allow for construction of a heat map of p-values based on these incremental changes. The tipping point analysis for this key secondary efficacy endpoint is displayed as a heat map. These results show that even in the unlikely case wherein all subjects in the placebo arm with missing data at Month 12 were categorised as responders, the seladelpar arm would still perform significantly better compared with the placebo arm. Overall, the results from these sensitivity analyses further support the results of the primary analysis of the corresponding key secondary efficacy endpoint. Sensitivity analyses, including complete case, treatment policy strategy, and control-based multiple imputation analyses, were performed to evaluate the other key secondary efficacy endpoint of changes in Pruritus NRS from baseline to Month 6 in subjects with baseline Pruritus NRS ≥ 4 (MSPN Analysis Set). The findings of the complete case analysis and the treatment policy strategy analysis were similar to those obtained in the primary MMRM analysis with imputed data, supporting the robustness of the beneficial effect of seladelpar on Pruritus NRS at Month 6. As a shift parameter of 1.5 was added to the imputed Pruritus NRS changes from baseline in the seladelpar treatment arm, the significant treatment effect became non-significant. However, since an increase of 1.5 in Pruritus NRS changes from baseline for

	all subjects with missing data in the seladelpar arm is very unlikely, the results from the primary analysis of this key secondary endpoint are confirmed. An additional sensitivity analysis of change from baseline in Pruritus NRS from Week 14 through Week 26 in the MSPN Analysis Set was performed. Overall, the results were similar to those of the primary analysis for the corresponding key secondary efficacy endpoint. Changes in monthly observed averages of Pruritus NRS from baseline to Month 6 in the MSPN Analysis Set were assessed as an additional sensitivity analysis. The results were consistent with the primary analysis for this key secondary endpoint, demonstrating greater decreases in monthly observed averages of Pruritus NRS in the seladelpar arm compared with the placebo arm.

2.6.5.3. Clinical studies in special populations

Not applicable.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Monotherapy

The majority of subjects in the seladelpar PBC studies received seladelpar as add-on therapy to UDCA, with approximately 5% of subjects receiving seladelpar monotherapy because of UDCA intolerance.

In study CB8025-32048 and study CB8025-31735, subjects who received seladelpar as monotherapy were assessed as a subgroup separately from those who received seladelpar in combination with UDCA. In study CB8025-31731-RE, the treatment effect of monotherapy was assessed as a subpopulation.

Data were also pooled for additional analyses of monotherapy subjects. Data were pooled and evaluated for the placebo-controlled studies, referred to as pool group I, and for the uncontrolled studies, referred to as pool group II:

- Pool group I combined placebo-controlled study CB8024-32048 and study CB8025-31735. Since the study design and key eligibility criteria for study CB8025-32048 and study CB8025-31735 are the same, baseline disease characteristics are expected to be similar between both studies and therefore the impact of the difference in allocation ratio on the validity of the pooling is considered minimal. For this pool group, data were presented for subjects who were randomised to placebo, seladelpar 10 mg, and any dose of seladelpar.
- Pool group II pooled uncontrolled studies. This pool group included subjects with PBC who were treated with seladelpar for the first time (including continuous seladelpar in an open-label study if treatment was initiated in a prior uncontrolled study).

For the monotherapy subpopulation, analyses were performed on pool group I at the Month 1 and Month 3 timepoints. Analyses were performed on pool group II at postbaseline timepoints Months 1, 3, 6, 9, and 12.

In study CB8025-32048, 12 subjects (6.2%) who were randomly assigned to study drug were UDCA intolerant, including 8 who received seladelpar 10 mg and 4 who received placebo. There was 1 subject

in the placebo arm who discontinued treatment early because of an AE that did not meet safety monitoring requirements.

In study **CB8025-31735**, 16 subjects (6.0%) who were randomly assigned to study drug were UDCA intolerant, including 6 and 8 who received seladelpar 5 and 10 mg, respectively, and 2 who received placebo.

In study **CB8025-31731-RE**, there were 7 subjects receiving monotherapy who entered after completing treatment in study CB8025-32048. There were 6 subjects (3.4%) receiving monotherapy who entered after participation in the legacy and CB8025-21838 studies. Among those subjects who completed treatment in study CB8025-32048, 6 had received seladelpar and 1 placebo. As of the data cutoff date for study CB8025-31731-RE, the applicant states that no subject receiving monotherapy had discontinued treatment.

Figure 19: composite biochemical response rate over time in the monotherapy subpopulations of study CB8025-32048 and study CB8025-31735

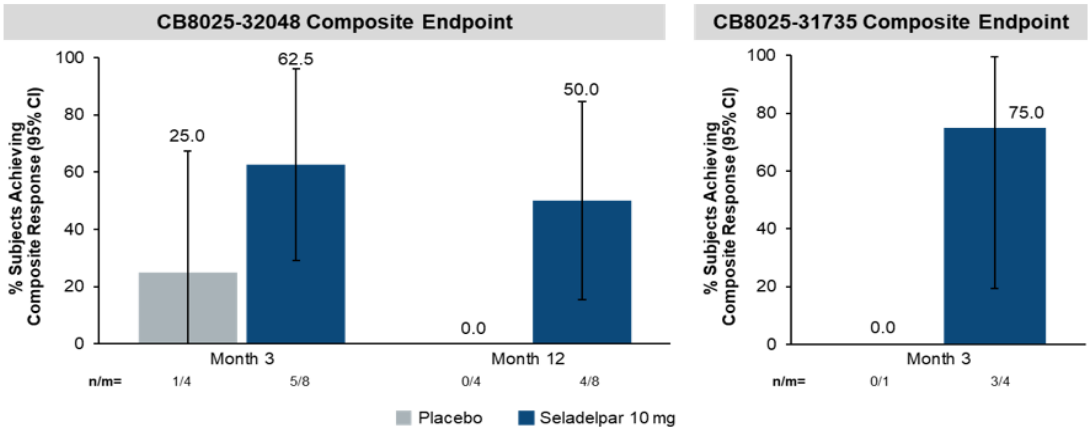
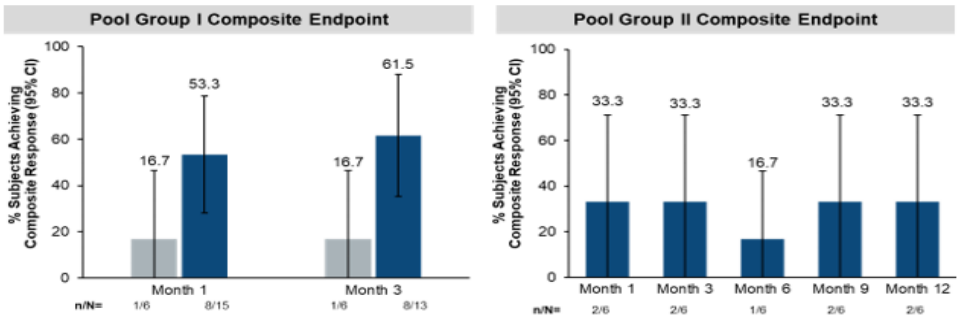


Figure 20: Composite biochemical response rate over time in the monotherapy subpopulations of pool group I and pool group II (ITT analysis set)



Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; ITT = intent-to-treat; m = number of response evaluable subjects; n = number of responders; N =number of evaluable subjects.
Composite response defined as ALP < 1.67× ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ ULN.
Pool Group 1 includes study CB8025-32048 and study CB8025-31735. Pool group II includes subjects who initiated treatment with seladelpar in an open-label study (CB8025-21629 [including rollovers to CB8025-31731], CB8025-31731, and CB8025-31731-RE [including subjects with prior participation in CB8025-21838]).
Source: Pooled Efficacy Analyses Table 14.2.1.3.1 and Table 14.2.1.4.1.

In pool group I, 3/16 (19%) achieved ALP normalisation compared with no subjects in the placebo arm.

Cirrhosis

Development of cirrhosis has been documented in approximately 12% to 17% of patients with PBC within 10 years of diagnosis (Corpechot 2002). Across the PBC programme, the effectiveness of treatment with seladelpar was evaluated in subjects who had cirrhosis at baseline. Subjects with cirrhosis were identified

based on criteria established for each study. In study CB8025-32048 and CB8025-31731-RE, cirrhosis were defined using the following criteria (one or more):
• Historical liver biopsy demonstrating cirrhosis (e.g., Ludwig Stage 4 or Ishak Stage 5)
• Current or prior history of decompensated liver disease, including ascites, hepatic encephalopathy, oesophageal varices, or other clinical conditions consistent with liver cirrhosis and/or PHT,
• Liver stiffness > 16.9 kPa by FibroScan at Screening
• Combination of platelets < 140× 10 3/μL with the following:
– Serum albumin < 3.5 g/dL
– INR > 1.3 (not due to antithrombotic agent use)
– Total bilirubin > 1.0× ULN
• The presence of radiological evidence of cirrhosis (nodular liver) with concurrent splenomegaly
• Clinical determination by the Investigator

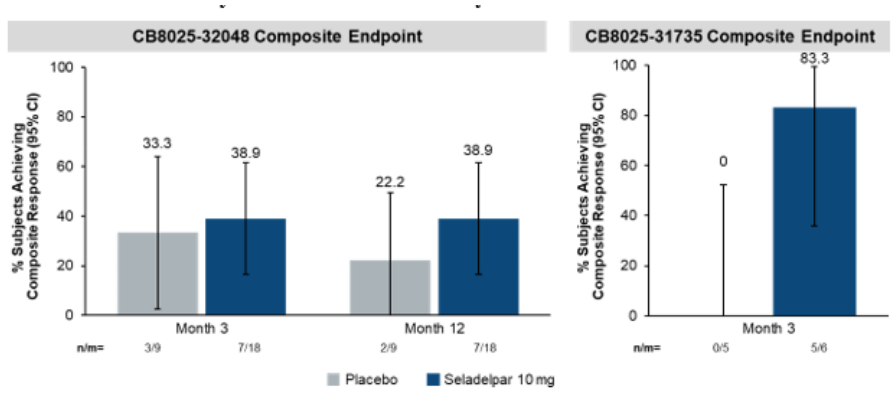
Data from study CB8025-32048 are a key source for assessing the efficacy of seladelpar in this population compared with placebo. Study CB8025-31731-RE, which used the same criteria for cirrhosis diagnosis as study CB8025-32048, provides the largest dataset of supportive data. Cirrhosis subpopulation data from other studies such as CB8025-31735 also support study CB8025-32048.

In study CB8025-32048, 27 subjects (14.0%) with cirrhosis at baseline were randomly assigned to study drug, with 18 assigned to receive seladelpar 10 mg and 9 assigned to receive placebo. There were 4 subjects with cirrhosis at baseline who discontinued treatment early, 1 subject (5.6%) in the seladelpar 10 mg arm and 3 subjects (33.3%) in the placebo arm. The subject who had received seladelpar 10 mg was lost to follow-up. In the placebo arm, 1 subject each (11.1%) discontinued treatment because of an AE associated with liver safety monitoring and an AE that did not meet safety monitoring requirements. A third subject was lost to follow-up.

In study CB8025-31735, 29 subjects (10.9%) with cirrhosis at baseline were randomly assigned to study drug, including 9 and 13 who received seladelpar 5 and 10 mg, respectively, and 7 who received placebo).

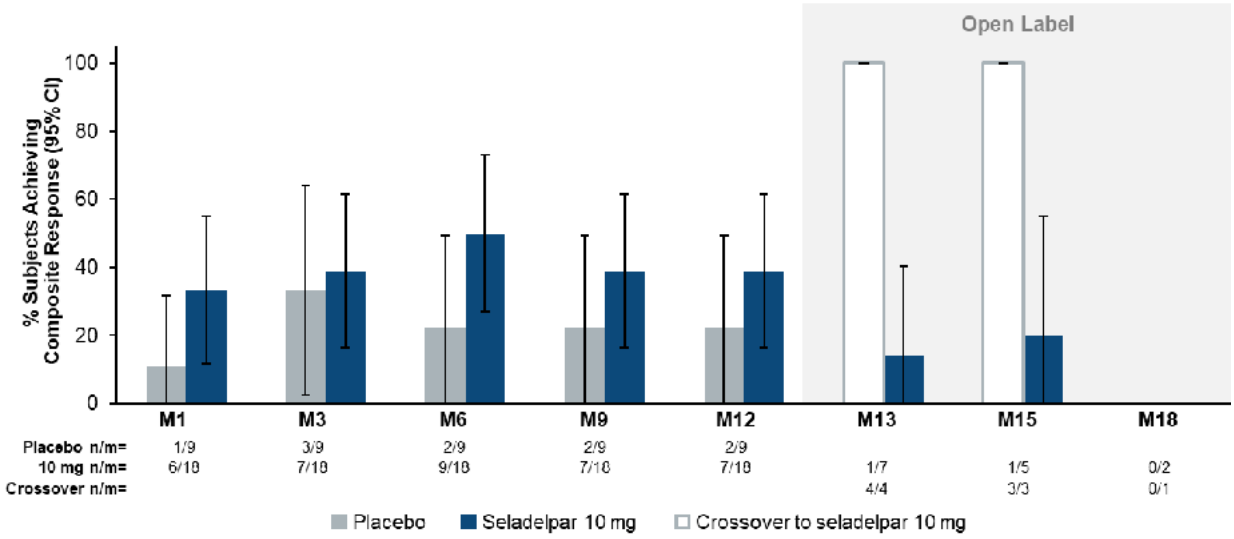
In study CB8025-31731-RE, there were 13 subjects (12.4%) with cirrhosis at baseline of study CB8025-32048 who completed treatment in study CB8025-32048 (9 subjects had received seladelpar and 4 placebo) and entered this study and a total of 33 subjects (19.0%) with cirrhosis at baseline who had participated in the legacy or CB8025-21838 studies. As of the 29 June 2023 data cutoff date for study CB8025-31731-RE, no subjects with cirrhosis who entered from study CB8025-32048 had discontinued treatment and 1 subject from the legacy and CB8025-21838 studies had discontinued treatment because of administrative decision by investigator, sponsor, or designee.

Figure 21: Composite biochemical response rate in the cirrhosis subpopulations of study CB8025-32048 and study CB8025-31735



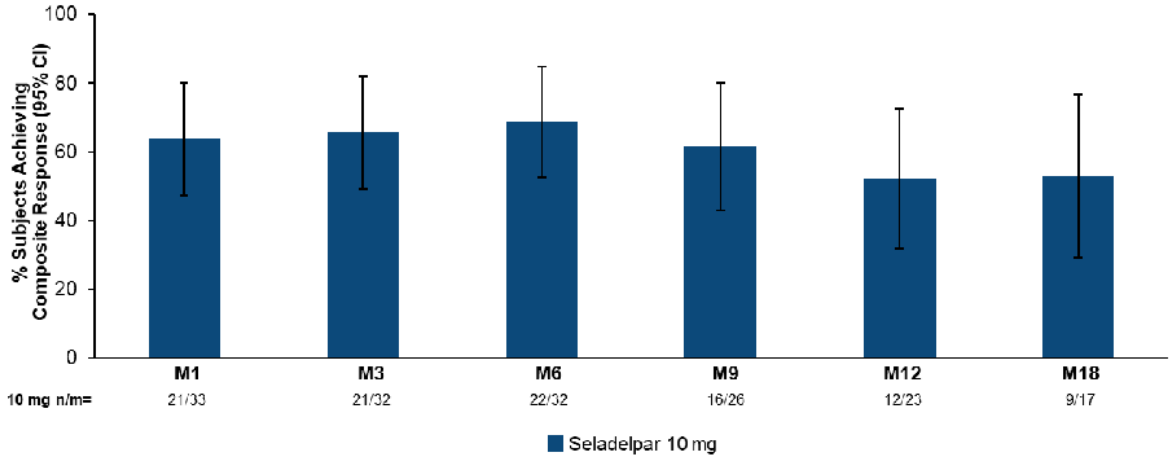
Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; ITT = intent-to-treat; m = number of response evaluable subjects; n = number of responders.
Composite response defined as ALP < 1.67× ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ ULN.
For study CB8025-32048 and study CB8025-31735, the primary endpoint was evaluated at Month 12 and Month 3, respectively. For study CB8025-31735, data are presented for the modified ITT Analysis Set. For study CB8025-32048, data are presented for the ITT Analysis Set. For CB8025-31735, seladelpar 5 mg arm not shown.
Source: Pooled Efficacy Analyses Table 14.2.1.6.2 and CSR CB8025-31735 Table 14.2.2.5.

Figure 22: Composite biochemical response rate over time in the cirrhosis subpopulations of study CB8025-32048 and study CB8025-31731-RE by study CB8025-32048 treatment assignment (ITT analysis set)



Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; ITT = intent-to-treat; m = number of evaluable subjects; M = month; n = number of responders.
Composite response defined as ALP < 1.67× ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ ULN.
Data collected during study CB8025-31731-RE were as of the data cutoff date of 29 June 2023. Months 13, 15, and 18 correspond to 1, 3, and 6 months, respectively, of open-label treatment with seladelpar in study CB8025-31731-RE.
Source: Pooled Efficacy Analyses Table 14.2.1.6.2.

Figure 23: Composite biochemical response rate over time in the cirrhosis subpopulation in study CB8025-31731-RE in subjects from legacy and CB8025-21838 studies (ITT analysis set)

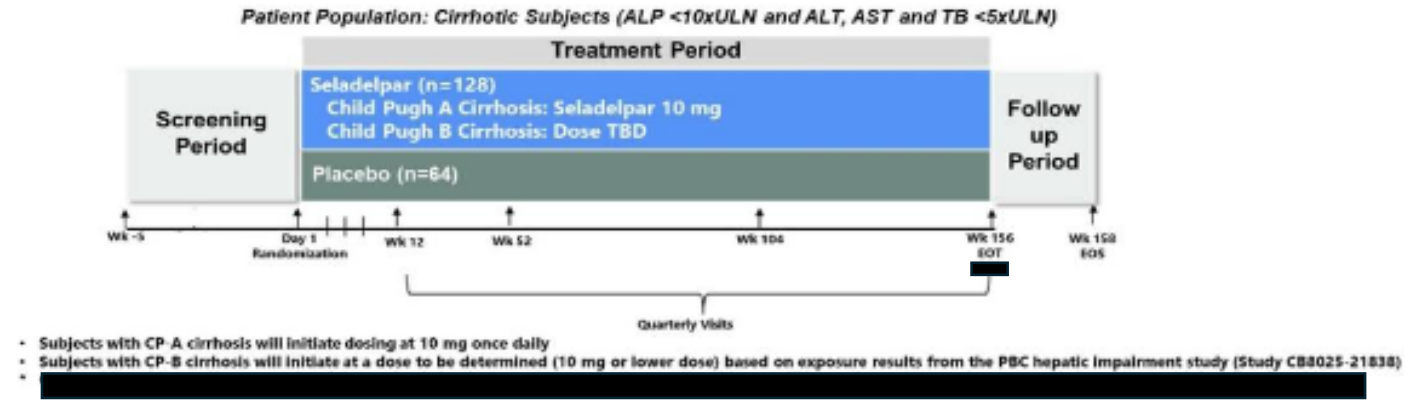


Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; ITT = intent-to-treat; m = number of response evaluable subjects; M = month; n = number of responders.
Composite response defined as ALP < 1.67× ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ ULN.
Legacy studies include CB8025-21629, CB8025-31735, and CB8025-31731. CB8025-31731-RE is an ongoing study and data are as of 29 Jun 2023. Data shown through Month 18.
Source: Pooled Efficacy Analyses Table 14.2.1.7.2.

According to the applicant, there are two ongoing studies in patients with cirrhotic disease; Study **CB8025-21838** has collected data in PBC patients with more advanced disease (CP-A/B). It is a currently ongoing 2-part, open-label, non-randomised, single (Part A) and multiple (Part B) oral dose study of ≤ 10 mg seladelpar in PBC subjects with cirrhosis and varying levels of hepatic impairment as determined by CP classification. As of the data snapshot date of 13 October 2023, Cohorts 1 (CP-A without PHT), 2 (CP-A with PHT) and 3 (CP-B) had been completed, while enrolment for Cohort 4 (CP-C) is ongoing.

In addition, study CB8025-41837 (AFFIRM) is currently ongoing, which is a 3-year fixed duration study that will be carried out in patients with compensated cirrhosis and PBC. According to the applicant, this will allow the collection of additional data in patients with advanced disease, including both markers of cholestasis and clinical outcomes.

A short summary of the study is provided below:



This is a multicentre evaluation of seladelpar, administered as a once-daily oral capsule, in a randomised, double-blind, placebo-controlled, parallel-group study in subjects with PBC. This fixed-

duration study (156 weeks) will randomise approximately 192 subjects across approximately 150 sites worldwide. The population to be studied is patients with PBC and compensated cirrhosis restricted to Child-Pugh (CP)-A or CP-B. Subjects with CP-A cirrhosis will be randomised to seladelpar 10 mg once daily or placebo. Subjects with CP-B cirrhosis will initiate at a seladelpar dose to be determined (10 mg or lower dose) based on data from the PBC hepatic impairment Study CB8025-21838. Enrolment of subjects with CP-A may occur first, with initiation of enrolment for CP-B after availability of data from Study CB8025-21838. If deemed safe by the Investigator, all subjects will Laboratory testing for liver biochemistry markers of disease will be undertaken. Subjects will be asked to complete the following:

Primary Objectives
Efficacy: To evaluate the effect of seladelpar compared to placebo on event-free survival (EFS). EFS is defined as the time from start of treatment to the first occurrence of any of the following adjudicated events up to Week 156:

- Death by any cause
- Liver transplantation
- Model for End-Stage Liver Disease (MELD) score ≥15 (see Appendix J)
- Ascites requiring treatment
- Hospitalisation for any of the following qualifying events:
  - Oesophageal or gastric variceal bleeding
  - Hepatic encephalopathy (as defined by a West Haven score ≥2)
  - Spontaneous bacterial peritonitis confirmed by white blood cell (WBC) count, differential, and/or inoculation of aerobic and anaerobic blood culture bottles via diagnostic paracentesis
- Progression to Child-Pugh (CP)-C

Approximately 192 subjects will be randomised (128 on seladelpar and 64 on placebo). Enrolment of subjects with TB <2×ULN will be capped at 60% of all subjects randomised 2:1 (seladelpar:placebo) Randomisation will be stratified based on baseline TB values (TB <2×ULN versus TB ≥2×ULN but <5×ULN. It is expected that approximately 192 subjects (2:1 ratio of seladelpar: placebo) are required to accrue at least 65 events, which provides approximately 80% power to detect a hazard ratio of (seladelpar relative to placebo).

Sample size calculations are based on the following: assumptions (1) a median EFS of years for the placebo group, based on an analysis from the GLOBAL PBC Study Group database of subjects with advanced PBC disease and cirrhosis on UDCA for at least 1 year assessing time to hepatic decompensation, hepatocellular carcinoma, liver transplantation, MELD>15, or death (data on file); (2) exponentially distributed EFS; and (3) an exponential loss to follow-up rate of /year for both treatment groups. It was further determined that a median EFS of approximately years would require % of the population to be in the TB <2×ULN strata (median EFS, years) and % in the TB ≥2×ULN but <5×ULN strata (median EFS, years) (data on file). An interim analysis will be conducted by an independent, unblinded statistical team using all EFS data collected up through and including the interim analysis cutoff date, defined as the date of the event. If conditional power at the interim analysis is in the "promising zone" (to <), then sample size is adjusted (i.e., increased) from a minimum of EFS events to a maximum of EFS events using a constrained promising zone approach. (Note: It is expected that approximately subjects are required to yield events when the hazard ratio is.). Otherwise, the number of events for the final analysis remains at EFS events.

2.6.5.6. Supportive study

Supportive Study CB8025-31731-RE (ASSURE)

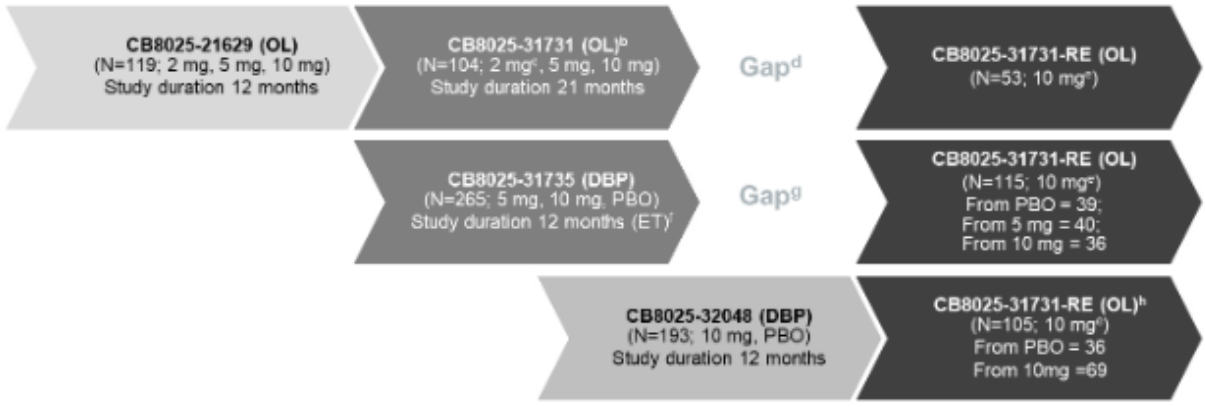
Study CB8025-31731-RE is an ongoing, long-term, open-label, phase 3 study in subjects with PBC who either completed the pivotal, placebo-controlled phase 3 study CB8025-32048 or the ongoing open label PBC hepatic impairment study CB8025-21838, or subjects who had participated in previous seladelpar PBC studies (phase 3 placebo-controlled study CB8025-31735 or long-term open-label study CB8025-31731, which included subjects from the phase 2 open-label study CB8025-21629; these studies are hereinafter referred to as **legacy studies**).

Subjects who entered CB8025-31731-RE from legacy or CB8025-21838 studies were grouped together for data summarisation. These subjects were analysed separately from the study CB8025-32048 parent group because subjects enrolled in study CB8025-31731-RE from the legacy studies had a treatment gap of > 1 year due to the early termination of study CB8025-31735 and study CB8025-31731 by CymaBay in 2019, and the small number of subjects entering study CB8025-31731-RE from hepatic impairment study CB8025-21838 had limited exposure to seladelpar (< 30 days) and variable time from completion of study CB8025-21838 and initiation of study CB8025-31731-RE.

The primary objective of the study is safety.

Efficacy assessments include markers of cholestasis (ALP, total bilirubin), pruritus, biochemistry laboratory parameters (including GGT, ALT, and AST), and PBC clinical outcomes.
Safety assessments include reporting of AEs; laboratory testing (haematology, biochemistry, pregnancy), vital sign measurements, ECGs, and physical examination.

Figure 24: Subject flow across PBC Studies of Seladelpar ≤ 10 mg (as of CB8025-31731-RE Snapshot)



Abbreviations: DBP = double-blind, placebo-controlled; ET = early termination; min = minimum; max = maximum; OL = open label; PBC = primary biliary cholangitis; PBO = placebo.

Subjects from the CB8025-32048 parent group are either continuing treatment with seladelpar or crossing over to treatment with seladelpar from placebo. Subjects receive seladelpar 10 mg once daily on entry into the study.

Data were analysed for subjects in study CB8025-31731-RE in the following ways:

- Subjects who were randomised to seladelpar 10 mg in study CB8025-32048 and continued treatment with seladelpar (i.e., continuous seladelpar subjects) and those who were randomised to placebo in study CB8025-32048 and initiated treatment with seladelpar in study CB8025 31731-RE (i.e., crossover subjects) were analysed. Data from both study CB8025-32048 and study CB8025-31731-RE were included; baseline is defined as that of study CB8025-32048.

- Subjects from parent studies CB8025-21629, CB8025-31731, CB8025-31735, or CB8025-21838 were analysed together. Subjects treated in the legacy studies (CB8025-21629, CB8025-31731, CB8025-31735) before entering study CB8025-31731-RE often had significant exposure to seladelpar before experiencing a treatment gap of > 1 year due to completion or early discontinuation of these studies. Because of the gap in treatment, previous treatment assignment was not considered for these subjects in the analyses for study CB8025-31731-RE, and all were considered functionally naïve to treatment on entry into study CB8025-31731-RE. Subjects from study CB8025-21838 had limited seladelpar dosing (< 30 days) before entering study CB8025-31731-RE and therefore data from study CB8025-21838 were not included in the analysis. Baseline for all subjects in this group is from study CB8025-31731-RE.

For each CB8025-31731-RE analysis group detailed above, the number and percentage of subjects who were treated and who discontinued treatment along with the reason for treatment discontinuation were presented by treatment group. Subject demographics and baseline disease characteristics were summarised by treatment group. For subjects whose extension study data were concatenated to the parent study, the baseline disease characteristics from the parent study were presented.

Table 38: Overall subject treatment disposition in study CB8025-31731-RE (safety analysis set)

Category	Seladelpar 10 mg in CB8025-31731-RE				Seladelpar Any Dose in CB8025-31731-RE (N=280) n (%)
	CB8025-32048 Parent Group		Legacy and CB8025-21838 Parent Group	Overall Seladelpar 10 mg (N=279) n (%)	
	Crossover Seladelpar (N=36) n (%)	Continuous Seladelpar 10 mg (N=69) n (%)	Seladelpar 10 mg (N=174) n (%)		
Subjects treated	36 (100)	69 (100)	174 (100)	279 (100)	280 (100)
Subjects completed study	0	0	0	0	0
Subjects who discontinued treatment	0	1 (1.4)	21 (12.1)	22 (7.9)	22 (7.9)
Primary reason for treatment discontinuation					
Administrative decision by PI, Sponsor or designee[a]	0	0	7 (4.0)	7 (2.5)	7 (2.5)
Any adverse events	0	0	7 (4.0)	7 (2.5)	7 (2.5)
Adverse events other than monitoring criteria[b]	0	0	5 (2.9)	5 (1.8)	5 (1.8)
Liver safety monitoring	0	0	2 (1.1)	2 (0.7)	2 (0.7)
Other	0	0	2 (1.1)	2 (0.7)	2 (0.7)
Withdrawal of informed consent	0	0	2 (1.1)	2 (0.7)	2 (0.7)
Discretion of investigator/Sponsor, noncompliance	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Lost to follow-up	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Pregnancy	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Required the use of prohibited concomitant medications	0	1 (1.4)	0	1 (0.4)	1 (0.4)

Abbreviation: PI = Principal Investigator.

Figure 25: Composite biochemical response rate for subjects in study CB8025-32048 and upon rollover to CB8025-31731-RE

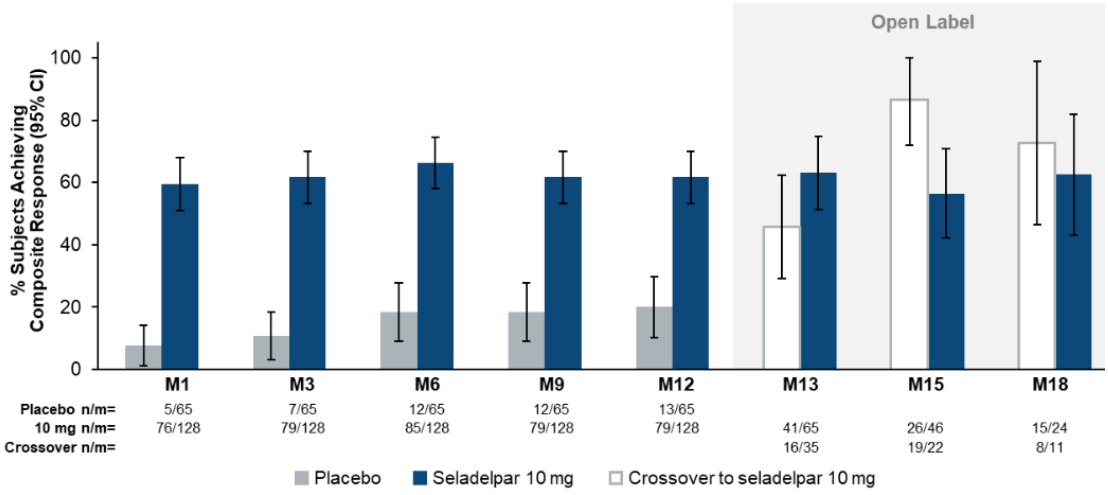
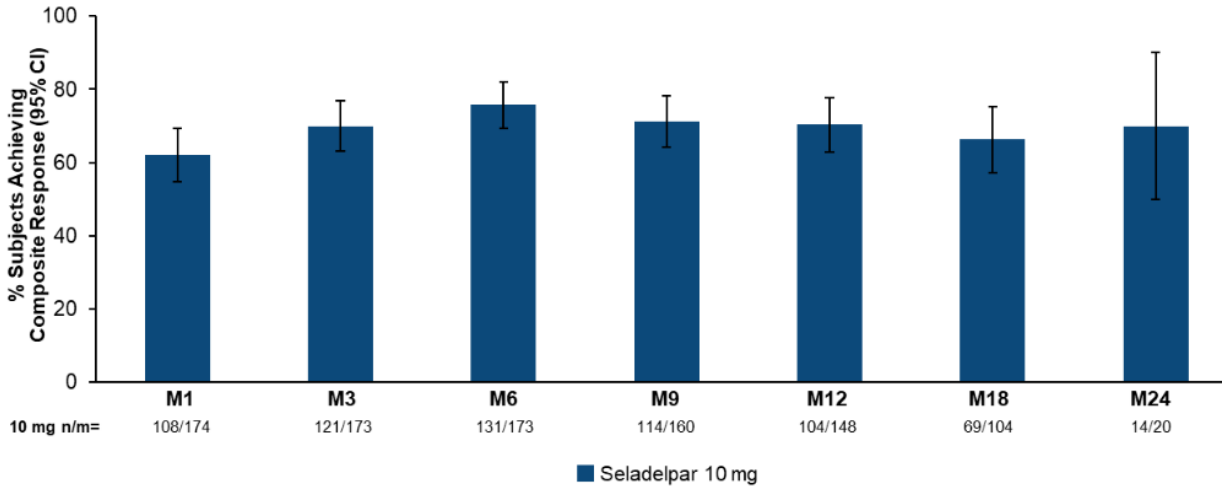


Figure 26: Composite biochemical response rate during CB8025-31731-RE in subjects from legacy and CB8025-21838 studies



Abbreviations: CI = confidence interval; n = number of responders; m = number of response evaluable subjects; M = month
Source: ISE Table 14.2.1.1.2.2

2.6.6. Discussion on clinical efficacy

This submission seeks approval for seladelpar for the following indication:

"Seladelpar Gilead is a peroxisome proliferator receptor delta (PPARδ) activator indicated for the treatment of primary biliary cholangitis (PBC) including pruritus in adults without cirrhosis or with compensated cirrhosis (Child-Pugh A) 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 indication was not considered acceptable by the CHMP since the mechanism of action is supposed to be part of 5.1 of the SmPC and references to study endpoints (i.e. including pruritus) should, in general, not be included in 4.1. Furthermore, the applicant approved the name "Seladelpar

Gilead" for this medicinal product for implementation. Hence the applicant amended their indication claim during the procedure as follows:

Seladelpar Gilead 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.

Design and conduct of clinical studies

Six clinical studies are included for efficacy analysis in this application; however, the focus will be on the pivotal phase 3 study RESPONSE (CB8025-32048), with supporting data from the prematurely terminated phase 3 study ENHANCE (CB8025-31735), the phase 2 study dose ranging study CB8025-21629, and interim results from the ongoing long-term follow up study ASSURE (CB8025-31731-RE).

Dose selection studies:

Initially, based on studies in healthy volunteers and in subjects with mixed dyslipidaemia, two higher doses were chosen (50 mg and 200 mg) for a phase 2 study in patients with PBC (CB8025-21528). Although leading to improvement in markers of cholestasis, the development of these doses was abandoned due to transaminase elevation. Instead, an open label study (CB8025-21629) was undertaken, examining the doses 2 mg, 5 mg and 10 mg, finally leading to evaluation of the 5mg and 10 mg doses in the placebo-controlled phase 3 study CB8025-31735 (ENHANCE).

Study CB8025-31735 (ENHANCE)

This was a phase 3 study with a double-blind, randomised, placebo-controlled 52-week dose-ranging parallel treatment group design. This study was planned to be a pivotal study but was terminated early due to safety findings in a concurrent phase 2 study of seladelpar in subjects with NASH. The study design, inclusion/exclusion criteria of the study population, stratification, primary and key secondary endpoint were discussed with CHMP during the prime process and are mostly in line with the pivotal study RESPONSE (CB8025-32048). However, in this study, subjects were randomly assigned 1:1:1 to study drug (placebo, 5 mg seladelpar (with up-titration after month 6 to 10mg in non-responders) or 10 mg seladelpar).

A total of 501 subjects were screened, and 265 subjects were randomised into the study (placebo=87, seladelpar 5 mg=89, and seladelpar 10 mg=89). As a result of the early study termination and the small number of subjects who had reached the 52-week timepoint (n=3), the timepoint for the primary and key secondary efficacy endpoints was amended to a 3-month timepoint before the study was unblinded. At the time of study termination, median duration of exposure to seladelpar was only around 16 weeks. At week 12, a total of 56, 56, and 55 subjects in the placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively, were evaluated. The response rate for the primary efficacy composite endpoint after 3 months of treatment was 12.5%, 57.1%, and 78.2% in the placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively. In addition, ALP was normalised in 27.3% of subjects treated with seladelpar 10 mg (95% CI: 16.1, 41.0, p<0.0001), which was higher compared to the placebo (0% [95% CI: 0, 6.4]) and seladelpar 5 mg (5.4% [95% CI: 1.1, 14.9], p=0.0839) groups. Regarding pruritus, the change from baseline pruritus NRS LS mean (SE) decreased by 1.55 (0.455), 2.01 (0.467), and 3.14 (0.455) in the placebo, seladelpar 5 mg, and seladelpar 10 mg groups, respectively; with the LS mean difference (95% CI) of -0.46 (-1.77, 0.84) for the seladelpar 5 mg group and -1.59 (-2.87, -0.30) for the seladelpar 10 mg group versus the placebo group. The difference was statistically significant for the seladelpar 10 mg group (p=0.0164) compared to the placebo group. However, due to the change in evaluated timepoint from 12 to 3 month and evaluated in a limited proportion of initially randomised patients (around 62%) because of the early termination of the study, efficacy results are regarded as supportive only.

Although both doses were statistically significant for both seladelpar groups when compared against placebo regarding the primary biochemical endpoint at month 3 (12.5% in the placebo group, 57.1% in the 5 mg group and 78.2% in the 10 mg group), the 10 mg dose was superior in reaching a normalised ALP and relieving pruritus, with a similar safety profile for both doses. Thus, the 10 mg dose was putting forward to the pivotal study.

Design and conduct of the pivotal study:

Pivotal Phase 3 study RESPONSE (CB8025-32048)

This was a phase 3, double-blind, randomised, placebo-controlled, multicentre study conducted in subjects with a diagnosis of PBC and an inadequate response or intolerance to UDCA. The study evaluated oral seladelpar 10 mg once daily versus placebo over 52 weeks. The study drug was given on top of UDCA in the majority of the subjects or as monotherapy if the patients were intolerant to UDCA.

The applicant calculated sample size for the primary endpoint as well as key secondary endpoints. The assumptions for the power calculations were based on results was study CB8025-31735. Even though the protocol was amended several times, no changes to the initial planned sample size occurred. No interim analysis was done in this study. A total of 360 subjects were screened and 193 were randomised, which was approximately what was estimated during the sample size calculation.

Eligible subjects in the RESPONSE study were 18-75 years old with PBC and should have an elevated ALP (ALP≥1.67xULN) despite an at least 1-year therapy with UDCA (or intolerance of UDCA). It is noticed that in order to not include patients with too severe hepatic disease, an upper cut off values for several hepatic biomarkers were included in the inclusion/exclusion criteria. Therefore, mainly an early stage PBC population is included. The exclusion of advanced PBC as defined by the Rotterdam criteria (albumin below the lower limit of normal AND total bilirubin above 1.0× ULN) will limit the proportion of patients with bilirubin above 1 at inclusion. PBC patients with decompensated hepatic impairment (Child-Pugh B or C) are also excluded from the trial, hence no efficacy will be established for this population. The EMA Reflection paper recommends inclusion of different PBC stages. Patients with moderately advanced disease were able to be included, thus also some patients with hepatic cirrhosis (Child Pugh A), and the applicant has reflected in the SmPC that no data are available in patients with evidence of decompensation or progression to Child-Pugh B or C hepatic impairment.

The randomisation procedure was performed centrally via an interactive web response system (IWRS) and was stratified by ALP level (<350 U/L versus ≥350 U/L) and the presence of clinically important pruritus NRS (<4 versus ≥4). No specific number of subjects was planned for each stratum.

The study report states that a total of 11 subjects (seladelpar 10 [7.8%]; placebo 1 [1.5%]) were categorised into an incorrect stratum at study entry in the IRT. It is unclear how many subjects were categorised into an incorrect stratum i.e. how many ended up in the ALP <350 U/L stratum when they should have been categorised into the ALP ≥350 U/L stratum and how many ended up in Pruritus NRS <4 contra Pruritus NRS ≥4 stratum. The applicant was asked to clarify and also justify whether the miss-classification of study treatment during randomisation (especially IP non-compliance) and miss-classification related to randomisation could have influenced the results. In response, the applicant stated that there was no impact on the study results due to miss-classification related to randomisation. A summary presenting the number of subjects that were miss-classified in each stratum was provided, which is appreciated. The impact of IP non-compliance on the results, in regard to the miss-classification was also discussed and it is accepted that is has not had an impact on the study results.

Study treatment appears to have been adequately blinded. Criteria for emergency unblinding were adequately outlined. No emergency unblinding was reported in the study.

The primary endpoint was a composite of cholestatic biomarkers (ALP and bilirubin) and the same endpoint has been used in previous studies for PBC, including Ocaliva, which achieved a conditional approval for PBC treatment 2016. Although the applicant has provided a thoroughly overview regarding literature data to support the validity of the biochemical primary endpoint to act as a surrogate for clinical endpoints, no new information is presented that contradict the statement in the EMA reflection paper regarding PBC that "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".

The primary composite endpoint as well as the key secondary endpoint were analysed as pre-specified in the SAP. Multiplicity was handled using a hierarchical testing procedure with overall alpha at 5%, which is acceptable.

Results for the number of subjects who achieved response for the composite endpoint as well as for Key secondary endpoint proportion of subjects with normalisation of ALP at 12 months are presented in the clinical study report. It is worth noting that the number as well as percentage of subjects who achieved response for each separate component were also presented in the report, which is in accordance with the *Points to consider on multiplicity issues in clinical trials, CPMP/EWP/908/99* and is therefore endorsed.

The applicant stated that any subject who did not provide an assessment, who discontinued treatment prior to the specified time point for response evaluation, or who otherwise had missing data were considered non-responder. A specification of the different events that led to non-response were requested, see further below.

Analysis of key secondary endpoint change from baseline in weekly averaged pruritus NRS at 6 months was done as pre-defined in the SAP. The model converged, therefore the initial pre-defined MMRM model was used, which is acceptable.

Cochran-Mantel-Haenszel test (used for primary composite endpoint and key secondary endpoint normalisation of ALP) and MMRM (used for key secondary endpoint pruritus NRS) model were adjusted for stratification variables baseline ALP level (< 350 U/L and >= 350 U/L) and baseline pruritus NRS (< 4 and >= 4). In order to judge what impact the randomisation miss-classification had on the analyses, the applicant was asked to provide results for both primary and key secondary endpoints, based on the original planned stratification for ALP (<350 U/L vs ≥350 U/L) and NRS (<4 vs ≥4). In response, the applicant stated that post-hoc analyses of the primary and key secondary endpoints using the randomisation stratification variables as entered in the IRT were performed. The conclusion was that there were some numerical differences when the additional post-hoc analyses were conducted based on the randomisation stratification variables instead of actual baseline values. However, the results of these post-hoc analyses were overall consistent with the results of the primary analyses of the primary and key secondary endpoints as presented in the CB8025-32048 CSR. The CHMP acknowledges the overall conclusion.

Analysis of key secondary endpoint change from baseline in weekly averaged pruritus NRS at 6 months was based on subjects in the MSPN analysis set. An additional exploratory analysis on key secondary endpoint; change from baseline in weekly averaged pruritus NRS at 6 months based on the ITT set

was pre-defined and done according to pre-specification. However, this exploratory analysis was not multiplicity controlled. For displaying the effect of seladelpar on pruritus on the whole population and not only for patients with a pruritus NRS score >=4 (MSPN analysis set) a multiplicity-controlled analysis based on the ITT set would have been preferred.

Results from the multiple pre-specified sensitivity analyses, validated the robustness of the primary endpoint as well as for Key secondary endpoint proportion of subjects with normalisation of ALP at 12 months. It is understood from the SAP that, control-based multiple imputation assumes that seladelpar subjects who discontinued from study are assumed to exhibit the same future evolution of the disease as those in the placebo group, both regarding biomarkers and pruritus. The applicant stated that since the number of seladelpar subjects who discontinued the study was small and very limited data was collected after treatment discontinuation, there were no strong supportive data to verify the assumption of long-term trend after treatment discontinuation. The applicant further stated that overall, it is intuitive to assume that once the active treatment is discontinued, the future evolution of the disease is similar to that in the placebo subjects who did not take active treatment. In addition, results from sensitivity analysis jump-to-reference for the primary endpoint as well as key secondary endpoints ALP normalisation and Pruritus NRS were consistent with the results in the CSR.

Analyses based on the Per-protocol set were not performed since the number of subjects in the ITT set was less than 5, which acceptable.

Primary biliary cholangitis clinical outcomes were defined as overall death; liver transplantation; MELD score ≥ 15 for at least 2 consecutive visits; ascites requiring treatment; and hospitalisation for new onset or recurrence of any of the following: variceal bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis. Subjects were assessed for PBC clinical outcomes by the Investigator. Clinical outcomes were hereafter adjudicated by an expert independent committee (CERC) (blinded to treatment assignment), that determined whether prespecified PBC clinical events definitions were met. Upon request, the applicant clarified that only in one case there were discrepancy between the investigator and the CERC, however the discrepancy did not change the outcome measure for the secondary endpoint of time to first occurrence of a PBC clinical outcome event.

Being a prime product, the applicant received protocol assistance on several occasions and in general, the advice given regarding the study design was followed, and are also in line with the EMA reflection paper regarding PBC. One exception is the study duration, where the applicant was encouraged to expand the study to two years instead of one in order to collect further placebo-controlled data on clinical endpoints. Unfortunately, this advice was not followed, and the reason provided by the applicant for not doing so is not fully agreed upon. Although it is agreed that an additional one-year placebo-controlled data would probably not collect sufficient number of clinical events to be able to see a significant difference between the placebo or seladelpar treatment, additional data regarding histology, a detectable (although not marked) progression of fibrosis and a doubled event rate would provide a better basis for a conclusion on the benefit/risk. Over 2 years, the imaging and biomarker endpoints may in addition provide further support.

Study population and disease characteristics:

In the pivotal study, a total of 360 subjects were screened and 193 subjects were randomised (seladelpar n=128, placebo n=65) and all received their intended study treatment. In the seladelpar arm, 117/128 (92%) completed the study and in the placebo group 57/65 (87.7%) completed the study treatment.

According to the protocol, study visits occurred in clinic, with the assistance of a home health service, or using virtual technologies according to the sites' determination. No visits using virtual techniques and home health services occurred during the study.

Most of the study subjects were females (95%), white (88%) and the mean age 57 years (range 28-75), which are in line with the known demographic profile for this patient group. Only around 20% were above 65 years. Although baseline demographics in general were balanced between the treatment groups, a difference in the proportion of subjects with Hispanic or Latino origin was seen, with 41.5% in the placebo group and 22.7% in the seladelpar group. In line with this, a difference was also seen in proportion of patients from Latin America (placebo=29%, seladelpar=19%) and North America (placebo=20%, seladelpar=39%). Upon request, the applicant conducted analyses to evaluate the efficacy results for the Hispanic/Latino vs non-Hispanic/Latino ethnic subgroups, as well as for subjects from Latin America vs North America vs rest of the world subgroups. As the applicant concludes, the effects of seladelpar were generally similar across evaluable ethnicity and region subgroups and the overall population; thus, ethnicity and region do not appear to be effect modifiers. This is agreed.

Regarding disease characteristics, the mean duration of PBC was 8.3 years and most patients had a mild (86%) or moderately advanced (14%) disease according to the Rotterdam Stage of Disease criteria. No patients had an advanced disease which is in line with the inclusion/exclusion criteria. A slight imbalance in the proportion of patients regarding the disease stage was seen between the groups with around 10% more patients having moderately advanced disease in the seladelpar group. The same pattern was seen in the fibrosis score, were 43% in the seladelpar group had a fibrosis score 2-4 compared with 34% in the placebo group. However, the proportion of patients with non-decompensated cirrhosis were similar in both groups, around 14%. Only 3 patients had portal hypertension, and these patients all were randomised to the placebo group. The small imbalance in the disease stage is not supposed to be of an advantage to the seladelpar group and thus this will not be further pursued.

Only a few patients were UDCA intolerant and received seladelpar as monotherapy (12 patients, 6.2%). The mean baseline total bilirubin concentration was less than or equal to the ULN in 87% of the enrolled subjects. Around 53 % of the subjects had a total bilirubin concentration >0,6 x ULN.

Mean pruritus NRS was 3.0 in both groups and among all enrolled subjects, 49 (38%) in the seladelpar arm and 23 (35%) in the placebo arm had moderate-to-severe pruritus (NRS ≥ 4) at baseline. Around 72% of the patients had a history of pruritus and around 7 % of the patients were treated with concomitant cholestyramine, with a slight difference between the groups (12% in the placebo group and 4.7% in the seladelpar group).

Efficacy data and additional analyses

79/128 (61.7%) in the seladelpar group and 13/65 (20%) in the placebo group achieved the composite biochemical primary endpoint ($p<0.0001$). This was mainly due to a reduction in the ALP value, both as a >15% decrease in ALP (84% seladelpar vs 32% placebo) and achieving an ALP <1.67xULN (66% seladelpar vs 26% placebo). The proportion of patients achieving a total bilirubin <1xULN was similar between the groups (81% seladelpar vs 77% placebo) which is not unexpected since most of the patients had normal bilirubin at screening. A higher proportion of response was seen in patients with a supposedly milder disease regarding ALP values (strata ALP <350 U/L + NRS <4 or ALP<350 U/L + NRS >4). As the applicant points out, this is not unexpected since it could be anticipated that it may be harder for subjects with higher ALP values to reach the predefined endpoint. In the stratum ALP >350 U/L + NRS<4, there were limited number of patients (9 placebo and 15 seladelpar treated subjects), thus no conclusion can be drawn regarding any lack of efficacy in that stratum. Upon request, the applicant also clarified that in the Stratum 3 (ALP ≥ 350 U/L and Pruritus

NRS < 4 at baseline) 80.0% (12/15) of subjects in the seladelpar group had a ≥ 15% reduction in ALP whereas the numbers in the placebo group were 55.6% (5/9). For the seladelpar arm, this was in consistence with the proportion of patients with ≥ 15% reduction in ALP in the overall ITT population (seladelpar 83.6%). This is seen as reassuring for the efficacy in the stratum, but numbers are low.

It was not fully clear how many patients that were non responder due to missing data, discontinuation of study drug or other reasons. The applicant clarified that among the 14 seladelpar subjects (10.9%) with missing Month 12 laboratory data, 11 had discontinued the study early (5 due to subject withdrawal, 3 due to AEs, 1 due to a protocol deviation, 1 due to loss to follow up, and 1 due to other reasons). The 3 remaining seladelpar-treated subjects had Month 12 laboratory samples collected outside of the pre-specified analysis window. The 8 placebo-treated subjects (12.3%) who were missing Month 12 laboratory data had discontinued the study early (2 due to subject withdrawal, 4 due to AEs, 1 due to a protocol deviation, 1 due to loss to follow up). The provided data do not evoke any further concern.

The first key secondary endpoint, normalisation of ALP, was reached in 32/128 (25%) of the seladelpar treated patients and in none (0%) of the placebo treated patients. Although only seen in 1/4 of the patients, this is an important finding since a normalisation of ALP in the clinic has been associated with an overall survival in line with the normal population. A significant decrease in ALP seems to occur already after one month although a normalisation took longer to occur (6-9 months).

Other endpoints examining the biomarkers (non-multiplicity controlled) using different cut-off values or timepoints of evaluation were in line with the primary results.

In addition, a decrease in other liver specific parameters such as GGT and ALT were seen in numerical favour of seladelpar.

Regarding the bilirubin value, although the majority had normal values at baseline, there seems to be a slight decrease in bilirubin (assessed as percent change from baseline) in especially the seladelpar population at month 6, however at month 12 the values seem to be back to baseline. Thus, it is not fully clear if seladelpar has the ability to affect also the bilirubin levels. As pointed out by the applicant, elevated bilirubin levels are strongly associated with bad outcome but usually occur later in the disease. However, there are indications from a recent publication from the Global PBC Study Group (Murillo Perez 2020) that a bilirubin threshold of 0.6 × ULN had the highest ability to predict liver transplantation or death at 1 year. This is also recognised in the EMA reflection paper on PBC where it is stated that "*An endpoint of complete response, i.e. normalisation of ALP and a bilirubin level of < 0.7xULN is highly recommended as a primary or secondary endpoint*. It is noticed that around half of the patients in the study had a bilirubin value above 0.6 x ULN at baseline.

To further find out if seladelpar also can affect the bilirubin levels, the applicant provided additional post hoc analysis: among subjects with total bilirubin ≥ 0.6× ULN at baseline, 14 (20.3%) of seladelpar and 5 (15.2%) of placebo subjects achieved a total bilirubin level < 0.6× ULN at Month 12. In addition, the percentage of patients in the seladelpar group who achieved a complete response at month 12 as defined by the EMA reflection paper (e.g., *normalisation of ALP and a bilirubin level of < 0.7xULN)* was 21.9% (28/128). None of the patients in the placebo group achieved this endpoint. However, the percent of subjects meeting the total bilirubin level of < 0.7× ULN component of the composite endpoint at Month 12 was 60.9% (78/128) and 56.9% (37/65) in the seladelpar and placebo groups, respectively. Thus, although the difference seen between seladelpar and placebo are mainly due to changes in ALP values, also a small change in the bilirubin values is evident.

The other key secondary endpoint, change from baseline to month 6 in weekly averaged pruritus NRS in patients with a baseline pruritus score of ≥4, was also significantly better in the seladelpar group

than the placebo group (LS mean (SE) -3.2 (0.28) vs -1.7 (0.41), difference -1.5 (-2.5, -0.5), P=0.0047).

Consistent with the results from the analysis of the key secondary efficacy endpoint of changes in Pruritus NRS at Month 6, results from exploratory endpoints such as LS mean changes in the Itch Domain of the PBC-40 QoL from baseline to Month 6 were -2.20 in the seladelpar arm vs -0.40 in the placebo arm and the LS mean change from baseline to month 6 in the total score of the 5-D Itch scale was -4.7 in the seladelpar arm compared with -1.3 in the placebo arm.

It is acknowledged that the worst pruritus NRS has been used in previous studies for several approved medications in other indications. There is, however, limited information regarding the validity of the worst itch NRS in the PBC population. The applicant has provided an analysis regarding content validity, which is appreciated, however, there is limited information regarding minimal important difference, and it is not clear if the difference between the placebo and the seladelpar group of -1.5 could be considered clinically relevant. Usually, a responder analysis endpoint is preferred and a reduction of ≥ 2-4 points is considered clinically relevant, at least in pruritic skin diseases. It is also noted that in the applicant's power calculation, a difference of ≥ 2 was expected. Upon request, the applicant provides a discussion regarding the clinical importance of the pruritus result in the studies. The applicant identified an improvement of 3 points or more as a clinically relevant change from a patient perspective. This assumption was based both on literature data and on data from patients interviewed by the applicant as part of NRS scale and electronic diary development. Thus, a change from baseline of 3.2 in the patient group would be regarded as a clinical important difference for that population. In the responder analysis provided (however non-multiplicity controlled), the proportion of patients achieving a decrease of NRS ≥ 2, ≥ 3 or ≥ 4 over time was in favour of Seladelpar Gilead. At month 6, the proportion of patients achieving a reduction of NRS ≥ 2 was nominal significantly higher in the seladelpar group (69.4%, CI 56.5, 82.3) versus the placebo group (30.4%, CI 11.6, 49.2). In addition, 44.9% and 28.6% of the Seladelpar Gilead patients and 21.7% and 17.4% of the placebo patients achieved a ≥3 and ≥4 points reduction of pruritus, although with slightly overlapping CIs. Thus, the numbers were in favour for the Seladelpar Gilead-treated group. It is acknowledged that the study was not powered for a responder analyses.

The anchoring analyses provided by the MAH, showing that 1-category improvement in PGI-S (that according to the applicant presents a minimal individual change that is meaningful to the patient) was associated with a median 2.93-point decrease in pruritus.

To conclude, the totally of data points towards an effect regarding pruritus that are clinically relevant.

In the overall population (ITT analysis set, exploratory endpoint), the mean baseline pruritus NRS value was 3.0 in both groups and at month 6, LS mean changes from baseline in weekly averaged Pruritus NRS in the seladelpar arm were -1.3, relative to -0.4 in placebo (nominal p=0.0001 for the LS mean difference). The clinical relevance of these findings is questioned, however since no claims regarding efficacy on pruritus in the overall population is made, this is not further pursued.

Of the patients with NRS >0 at baseline (seladelpar=98, placebo=50), only a few patients achieved a NRS=0 at month 6, with a similar proportion in the seladelpar and placebo groups (16% vs 12%). Additional provided analysis showed that at Month 6, among subjects with Pruritus NRS = 0 at baseline, 6.7% (2/30) and 20% (3/15) had Pruritus NRS > 0 in the seladelpar and placebo groups, respectively. In the ITT population, 14.1% (18/128) of seladelpar and 30.8% (20/65) of placebo subjects had a worsening in Pruritus NRS from baseline at Month 6. It is agreed with the applicant that these additional analyses demonstrate that a higher proportion of subjects treated with placebo compared with seladelpar experienced a worsening of pruritus at Month 6.

Pruritus is common during the course of the diseases and currently, no treatment is consistently approved across the EU for the symptomatic treatment of cholestatic pruritus in PBC, and current approved products have no effect or could even aggravate this symptom. Bile sequestrants are widely used as first-line therapy although limited evidence and are approved in some EU countries but other treatments are used off label. Around 7 % of the patients were treated with concomitant cholestyramine (12% in the placebo group and 4.7% in the seladelpar group) but it was not clear whether any of the patients had any other medication for pruritus received any additional rescue treatment for pruritus during the study and how this was handled in the analysis. Upon request, additional information regarding concomitant pruritus medication was provided. The applicant reported that 36.7% (18/49) of subjects in the seladelpar group and 47.8% (11/23) of subjects in the placebo group with moderate to severe pruritus (NRS ≥ 4) were on anti-pruritus medications at baseline. Upon request, sensitivity analyses were provided indicating that antipruritic medications at baseline or changes to antipruritic treatment during study did not impact the effect of seladelpar on pruritus.

In addition, some of the medications, for example rifampicin and cholestyramine, that are used for treatment in PBC-associated pruritus may reduce the effect of Seladelpar Gilead. To understand the overall itch-reducing effect seen with Seladelpar Gilead and to provide the appropriate information in the SmPC, additional information regarding these medications were provided. There were only a few patients who received a combination of Seladelpar Gilead and cholestyramine (5 patients) or rifampicin (4 patients) and no conclusion could thus be drawn regarding efficacy in these patients. However, information regarding possible interactions with these medications was regarded as important to provide to the prescriber and thus this was included in section 4.5 of the SmPC see also clinical pharmacology section).

There are limited results regarding any impact on disease progression, which is not surprising being a one-year study in a patient group with mostly mild disease regarding liver engagement.

Only one subject (a cirrhotic patient in the seladelpar arm) was positively adjudicated as having experienced PBC clinical outcome events, which was hospitalisation due to variceal bleeding and worsening of liver cirrhosis due to decompensated PBC on Study Day 379.

Regarding liver stiffness (measured by fibroscan) mean change from baseline was 0.24 kPa (4.58% change) for subjects receiving seladelpar relative to 1.34 kPa (9.87% change) for those receiving placebo at month 12. Since almost all patients had normal scans at baseline, the small numerical difference is not regarded as clinically relevant.

Regarding ELF score, there were no notable differences in mean values (or the components) for the seladelpar arm compared with placebo over the course of the study.

Regarding liver histology, forty-three subjects (22.3%) from study CB8025-32048 contributed samples at both baseline and Month 12 (paired samples), and 21 subjects (12% of the legacy and CB8025-21838 subjects) from the CB8025-31731-RE study contributed paired samples. At baseline in study CB8025-32048, a numerically higher percentage of subjects in the seladelpar arm had cirrhosis relative to the placebo arm (20.0% vs 11.1%). The data do not point towards any beneficial effect regarding histology changes in the seladelpar treated patients, however there were neither any signs of any detrimental effects.

Baseline values were similar across treatment arms for both the GLOBE and the UK-PBC risk scores but there seems to be a trend towards a decreased risk of clinical outcomes in both scores in favour of the seladelpar group. However, these scores are mainly based on changes in biomarkers and the clinical relevance of these findings are not clear.

Since there are limited information pointing towards a beneficial effect in hard clinical endpoints such as liver survival or progression of cirrhosis, and in the light of the biochemical response not being fully

approved as a surrogate for clinical hard endpoints, the applicant was asked to discuss whether any additional information regarding this could be provided within this procedure (new evidence regarding surrogacy, additional results regarding hard clinical endpoints from the long term study or the ongoing AFFIRM study)**.** No new substantial data has been provided supporting that a beneficial effect on biomarker can serve as surrogates for clinical events. Therefore, the submitted data was not considered as comprehensive and the CHMP asked the applicant to justify a conditional approval with the already ongoing AFFIRM study as a SOB (see benefit risk discussion).

Regarding the prespecified subgroups, efficacy was in general in favour of seladelpar regarding the primary and the two key secondary endpoints although in some subgroups, the numbers were too small to make any firm conclusions. For patients with a more severe disease (such as ALP ≥350 U/L, cirrhotic disease, TB >1), efficacy seems however to be lower, which is not unexpected since this patient group is regarded as more difficult to treat in the clinic.

Cirrhotic patients

In the pivotal study, 27 subjects (14.0%) with cirrhosis at baseline were randomised to receive seladelpar (n= 18) or placebo (n=9). The definition of liver cirrhosis was predefined with 5 different criteria used. Upon request, the applicant provided information that there were 11/27 (41%) patients who fulfilled only one criterion for cirrhosis. There were no subjects who met cirrhosis criteria based on laboratory findings alone and a minor part of the cirrhosis diagnosis was based on clinical determination by the Investigator only. This is acceptable. All but four patients completed the study and 7/18 (39%) in the seladelpar group and 2/9 (22%) in the placebo group achieved a biochemical response. Although it is expected that cirrhotic patients may have a lower response, the placebo response were in line with non-cirrhotic patient and are somewhat unexpected. However, the results are based on a few numbers of patients so this will not be further pursued.

In study CB8025-31735, the definition of cirrhosis was up to the treating physician. In that study, 29 patients with cirrhosis were included and 13 patients were randomised to seladelpar 10 mg and 7 to placebo. At month 3 only 6/13 patients in the seladelpar group and 5/7 patients in the placebo group seems to be available for evaluation of the biochemical response. It was not clear whether the additional 9 patients did not reach 3 months of treatment due to the premature termination of the study or if there were other reasons such as AEs or loss to follow up. Upon request, the applicant clarified that all missing ALP and bilirubin data at Month 3 were due to early study closure. However, 5 of the included 13 patients (38%) achieved a biochemical response in the seladelpar group in that study, which is in line with the result from the pivotal study.

Due to the different definition of cirrhosis in the two studies, no pooling of data between the studies have been made. This is acceptable, however the lack of a uniform definition of cirrhotic patients makes a full evaluation difficult.

13 patients with cirrhosis from the pivotal study and 33 patients from the other studies continued to the OL CB8025-31731-RE study. However, observed values on the biochemical parameters seems to be available only for a few patients beyond one year from the pivotal study and of the 33 patients that continued to the OL CB8025-31731-RE study from the other studies, 12 were reported responders at month 12 (36%), which is in line with the result from the pivotal study. According to the applicant, all cirrhotic patients, except one, were still in the study at data lock point.

It is noted that only a few patients (n=3) with portal hypertension (PHT) were included in the pivotal study for seladelpar, all randomised to the placebo group. However additional patients were included in the follow up study, from the other studies, thus receiving OL seladelpar. In the HI-study (CB8025-21838), patients with Child-Pugh A cirrhosis and PHT had a higher exposure for the drug than cirrhosis patients without PHT. Based on the limited efficacy results seen in the cirrhotic patient, and the

potential risk of a harmful effect in especially cirrhotic patients with PHT, the applicant was asked to provide additional information regarding safety in this population (Child-Pugh A cirrhotic patients with or without a high risk of decompensation). This is discussed in the safety section.

It is acknowledged that the applicant has 2 ongoing studies in patients with cirrhotic disease; Study CB8025-21838 has collected data in PBC patients with more advanced disease (CP-A/B). It is a currently ongoing 2-part, open-label, non-randomised, single (Part A) and multiple (Part B) oral dose study of ≤ 10 mg seladelpar in PBC subjects with cirrhosis and varying levels of hepatic impairment as determined by CP classification. As of the data snapshot date of 13 October 2023, Cohorts 1 (CP-A without PHT), 2 (CP-A with PHT) and 3 (CP-B) had been completed, while enrolment for Cohort 4 (CP-C) is ongoing.

In addition, study CB8025-41837 (AFFIRM) is currently ongoing, which is designed as a multicentre, placebo-controlled time-to-event study with up to a 3-year maximum observation period for each patient. The population to be studied is patients with PBC and compensated cirrhosis restricted to Child-Pugh (CP)-A or CP-B. Subjects with CP-A cirrhosis will be randomised to seladelpar 10 mg once daily or placebo. Subjects with CP-B cirrhosis will be randomised to seladelpar 5 mg once daily or placebo. Randomisation will be stratified based on baseline TB values (TB <2×ULN versus TB ≥2×ULN but <5×ULN. The primary objective of the study will be to evaluate the effect of seladelpar compared to placebo on event-free survival (EFS) where EFS is defined as the time from start of treatment to the first occurrence of any of the following adjudicated events up to Week 156: Death by any cause**,** Liver transplantation**,** (MELD) score ≥15**,** Ascites requiring treatment or Hospitalisation for any of the following qualifying events: (Oesophageal or gastric variceal bleeding, Hepatic encephalopathy, Spontaneous bacterial peritonitis, Progression to Child-Pugh (CP)-C).

Upon request, additional information regarding the study CB8025-41837 (AFFIRM) was provided by the applicant. The study is currently ongoing and started on 29 June 2023. Until November 2024, study participants have been enrolled at study sites in countries. An update of the study protocol has been provided with a re-estimated sample size based on a more conservative hazard rate estimate and annual drop out-rate. Sample size has thus been increased from 192 subjects (with estimated events) to 318 subjects (with estimated events). The applicant still wants to retain the 2:1 randomisation ratio due to factors such as enrolment challenges and ethical consideration. According to the applicant, there is a limited increase in sample size with 2:1 randomisation necessary to achieve the same power compared with 1:1 randomisation. This is acknowledged, however the previous raised concerns regarding the risk of dropouts and discontinuation of especially the placebo patients due to the approval of seladelpar and other treatments are still obvious. The applicant has however provided a strategy to mitigate this risk, that includes recruiting patients at sites with a later launch of the commercial drug, inclusion of more study sites and together with the updated sample size, this is acceptable although it is anticipated that the study will be ongoing for several years. Although it cannot be determined with certainty how long it will take to collect the specified events, the applicant provided an acceptable due date (August 2030) and included the description of the study in Annex 2 of the SmPC.

The applicant maintains plans for an interim analysis to assess the treatment effect and allow for potential sample size re-estimation, given the uncertainty regarding the observed treatment effect. The interim analysis will be conducted when % of the planned events have occurred. This is acceptable. The applicant has also incorporated a definition of the estimand and intercurrent event in the protocol, which is appreciated. But will need further consideration.

The primary objective of the study will be to evaluate the effect of seladelpar compared to placebo on event-free survival (EFS) were EFS is defined as the time from start of treatment to the first occurrence of any of the following adjudicated events up to Week 156: Death by any cause, Liver

transplantation, (MELD) score ≥15, Ascites requiring treatment or Hospitalisation for any of the following qualifying events: (Oesophageal or gastric variceal bleeding, Hepatic encephalopathy, Spontaneous bacterial peritonitis, Progression to Child-Pugh (CP)-C). The applicant implemented measures in the protocol to ensure adequate enrolment and data generation such as a more conservative hazard rate estimate and annual drop-out rate and a required elevated baseline ALP to ensure higher risk of clinical events. The applicant has also provided a comprehensive strategy to address potential recruitment delays. This is considered acceptable by the CHMP.

The applicant is however advised to submit the protocol post authorisation for agreement by the CHMP taking into consideration the below:

- There seem to be a mix up between estimands and estimation in the current study protocol. Some of the points listed as intercurrent events may rather relate to missing data, depending on what is expected to be the cause of treatment discontinuation.
- For the hypothetical strategy collected data after the intercurrent event is considered to be missing (where it is available or not) and then modelled using statistical methods. How it is modelled should be based on clinical considerations and pre-specified; however, there is currently no information how this is planned to be done. Furthermore, no details with respect to the tipping point analysis is given.
- In summary, leaving critical details ('critical' for interpretation of the results therefore for regulatory decision-making) to be described in the SAP may open the door to data-driven statistical choices. The applicant is therefore recommended to apply for EMA protocol assistance for further discussions concerning the choice of estimands before submitting the protocol for agreement.

Regarding monotherapy

Only 12 patients (6.2%) with intolerance to UDCA (and given seladelpar as monotherapy) were included in the pivotal study; 8 received seladelpar and 4 received placebo. It is acknowledged that UDCA intolerance is uncommon (4-6%) and the low number included is thus not unexpected. Additional information is provided from the CB8025-31735 study, where 8 patients received seladelpar and 2 received placebo. In the pooled analysis concerning these 22 patients (16 seladelpar and 6 placebo patients) around 50% (8 patients) of the seladelpar treated patients achieved a biochemical response at month 1 and month 3. In the placebo group, 1/6 (17%) achieved a biochemical response. Although based on a low number, based on the provided results, there are no reason to believe that efficacy is different for patients receiving seladelpar monotherapy and extrapolation to the results in the overall population should be possible.

Long-term efficacy results

Patients who completed the pivotal study CB8025-32048 were able to continue to the ongoing open label study CB8025-31731-RE, where all patients received seladelpar 10mg. The primary objective of the study is safety, although some efficacy endpoints is collected. Additional information from this study was provided by the applicant that verified that of the patients who completed the pivotal study (n=175), only 16 patients did not continue to the OL study (9 patients from Russia due to operational complexities, and 7 patients did not consent to participate in the OL study). The baseline characteristics of the subjects who enrolled in the OL study were generally similar to the baseline characteristics of the subjects at the start of Study CB8025-32048.

In addition, of the 109 patients that had a biochemical response at month 12, 86 patients (79%) still had a response after additional 12 months. This is reassuring. Of the 35 subjects initially randomised to seladelpar in study CB8025-32048 who did not meet the composite endpoint at Month 12, only 5 met

the composite endpoint for at least one timepoint in the second year of treatment while in study. Despite this, mean ALP decreased. Since the non-responders at Month 12 continue to show decreases in ALP, it is agreed with the applicant that a specific timepoint on when to stop treatment may not be necessary to define in the SmPC but could instead be left to the treating physician to decide on individual basis.

Additional 174 patients on seladelpar 10 mg treatment were also included in the follow-up study, recruited from other previous terminated studies or dose-ranging studies. Although OL, one year data on these patients are in line with the data from the pivotal study.

No patients in the follow-up study had any PBC clinical outcome event. However, data regarding efficacy beyond one year is limited and no conclusion can be made from the data provided by the applicant. Thus, the applicant has deleted any claims regarding efficacy beyond the time point of one year from the SmPC.

Additional efficacy data needed in the context of a conditional MA

The demonstrated beneficial effect of Seladelpar Gilead in the treatment of PBC is mainly based on a biochemical surrogate endpoint that has a reasonably likelihood to translate into benefits in terms of clinical outcomes.

The applicant has initially applied for a full marketing authorisation claiming that the submitted data can be considered as comprehensive. This was not agreed by the CHMP considering that the clinical relevance of the effect seen on biochemical response in relation to liver related endpoints needs to be confirmed for Seladelpar Gilead.

Accordingly, the applicant commits to provide comprehensive clinical data post authorisation based on the currently ongoing AFFIRM (CB8025-41837) study. This is a placebo-controlled, event driven study, with a maximum of 3-year duration for each participant that will be carried out in patients with compensated cirrhosis and PBC. The primary objective of the study will be to evaluate the effect of seladelpar compared to placebo on event-free survival (EFS) were EFS is defined as the time from start of treatment to the first occurrence of any of the following adjudicated events up to Week 156: Death by any cause, Liver transplantation, (MELD) score ≥15, Ascites requiring treatment or Hospitalisation for any of the following qualifying events: (Oesophageal or gastric variceal bleeding, Hepatic encephalopathy, Spontaneous bacterial peritonitis, Progression to Child-Pugh (CP)-C). Based on the provision placebo-controlled data on these clinical outcomes the efficacy of Seladelpar Gilead is expected to be confirmed.

2.6.7. Conclusions on the clinical efficacy

The applicant demonstrated a statistically significant improvement in pruritus for the treatment of PBC with Seladelpar Gilead. Despite the lack of an adequate validation in the PBC population, the score is considered useful to evaluate itch also in PBC, and a decrease of ≥3 points could be considered a meaningful important difference. A responder analysis carried out by the applicant, non-multiplicity controlled, showed that 44.9% of the Seladelpar Gilead treated patients and 21.7% of the controls achieved a ≥3 points reduction of pruritus. It is acknowledged that the study was not powered for a responder analyses.

In the overall population (ITT analysis set, exploratory endpoint), the mean baseline pruritus NRS value was 3.0 in both groups and at month 6, LS mean changes from baseline in weekly averaged Pruritus NRS in the seladelpar arm were -1.3, relative to -0.4 in placebo. Of the patients with NRS >0 at baseline (seladelpar=98, placebo=50), only a few patients achieved an NRS=0 at month 6, with a similar proportion in the seladelpar and placebo groups (16% vs 12%). Thus, not all patients may respond similarly to the pruritus reducing effect, but a clinically relevant effect is agreed.

A robust statistically significant effect is seen in biochemical values, which are considered a surrogate reasonably likely to translate in clinical outcomes. The applicant committed to provide comprehensive data on clinical outcomes post authorisation by means of the AFFIRM study which was made SOB to the conditional marketing authorisation.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

Description	Due date
In order to confirm the efficacy and safety of seladelpar in 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, the MAH shall conduct and submit the final results of the phase III randomised, placebo-controlled clinical study (AFFIRM) to evaluate the efficacy and safety of seladelpar on long-term clinical outcomes in adults with Primary Biliary Cholangitis (PBC) and compensated cirrhosis according to an agreed protocol	August 2030

2.6.8. Clinical safety

The primary evidence for safety of seladelpar 10 mg in the proposed indication is based on the phase 3, double-blind, randomised, placebo-controlled pivotal study CB8025-32048, conducted in subjects with PBC who had inadequate response or intolerance to UDCA. Additional supportive safety data in PBC comes from two phase 2 (CB8025-21528, CB8025-21629) and three phase 3 studies (CB8025-31735, CB8025-31731 and CB8025-31731-RE) in subjects with PBC.

Pivotal study CB8025-32048

The primary evidence of the safety of seladelpar in the proposed indication PBC is provided from the phase 3, double-blind, randomised, placebo-controlled pivotal study CB8025-32048 (RESPONSE). The study evaluated oral seladelpar 10 mg once daily versus placebo. A total of 193 subjects were randomised on a 2:1 basis and treated with seladelpar 10 mg once daily (128 subjects) or matching placebo (65 subjects).

The Rotterdam disease stage reflected mild disease in the majority of subjects (82.8% in the seladelpar 10 mg group, and 92.3% in the placebo group), and no subjects were enrolled with a Rotterdam score reflecting advanced disease.

Supportive studies

In supportive study CB8025-31735, a phase 3, double-blind, randomised, placebo-controlled, dose-ranging study evaluating seladelpar 5 mg and 10 mg versus placebo administered orally, a total of 265 subjects were randomised on a 1:1:1 basis and treated with seladelpar initial dose 5 mg: 89 subjects, 10 mg: 89 subjects, placebo: 87 subjects. Also, for this study, the majority of subjects had mild PBC.

The supportive phase 3 study CB8025-31735 was terminated early due to suspicious findings in a study on NASH (CB8025-21730) which were later resolved, with mean duration of exposure similar between the placebo (17.8 weeks), seladelpar 5 mg (17.6 weeks), and seladelpar 10 mg (17.6 weeks) treatment groups. Thus, with the shorter exposure, this study is not considered to be appropriate for long-term safety analyses and should be excluded from discussions on long-term safety.

2.6.8.1. Patient exposure

Overall, 1452 subjects were included in clinical studies, of which 293 subjects received placebo, and 1159 subjects received at least 1 dose of seladelpar. These subjects include both PBC patients, patients with other diagnoses and healthy controls.

Table 39: Study drug exposure (all seladelpar studies, safety analysis set)

	Overall		Clinical Pharmacology Studies		Controlled Double-Blind PBC Studies		Uncontrolled Open-Label PBC Studies	Other Indications	
n	1452		376		496		355	378	
	PBO	**SEL**	**PBO**	**SEL**	**PBO**	**SEL**	**SEL**	**PBO**	**SEL**
n	293	1159	39	337	165	331	355	89	289
Treatment Duration (Weeks)									
Mean	22.7	39.1	0.8	0.5	29.0	29.2	75.9	20.6	29.5
(SD)	(20.4)	(49.7)	(1.2)	(0.8)	(19.3)	(19.8)	(62.6)	(19.9)	(21.5)
Median	12.0	15.0	0.1	0.3	26.9	26.3	65.3	8.3	19.6
Min	0.1	0.3	0.1	0.1	1.3	0.1	0.1	2.1	0.1
Max	63.1	272.6	3.0	3.0	55.4	54.7	272.6	63.1	62.3

PBO = Placebo, SEL = Seladelpar, SD = standard deviation
Notes: The following studies were included: Clinical pharmacology studies: NAP-1001 (SAD and FE), NAP-1002 (MAD), CB8025-11941 (FE), CB8025-11734 (ADME), NAP-1005 (formulation), CB8025-11836 (formulation), CB8025-11942 (renal impairment), CB8025-11732 (hepatic impairment), CB8025-11733 (cardiac repolarisation), NAP-1003 (DDI), NAP-1004 (DDI), CB8025-11840 (DDI). Controlled double-blind studies (subjects with PBC): CB8025-21528, CB8025-31735, CB8025-32048. Uncontrolled open-label studies (subjects with PBC): CB8025-21629, CB8025-31731, CB8025-31731-RE (data cutoff date: 29 Jun 2023), and CB8025-21838 (data cutoff date: 16 May 2023). Other indications (completed studies): CB8025- 21730 (non-alcoholic steatohepatitis), CB8025-21427 (homozygous familial hypercholesterolemia), M8025-20711 (mixed dyslipidaemia). Overall: Includes all the unique subjects from all the studies listed.
Treatment groups: Placebo: subjects who received placebo. Seladelpar: subjects who received seladelpar at any dose.
Total exposure duration was calculated as the sum of exposure duration in each study. Any treatment gaps between studies are not included.

A total of 533 PBC subjects received at least 1 dose of seladelpar across placebo-controlled and uncontrolled studies in PBC, including 282 subjects who received seladelpar 10 mg from the start. Excluding the gap in treatment between studies, mean (SD) duration of seladelpar treatment at any dose was 68.69 (57.12) weeks (range: 0.14 to 272.57 weeks).

The number of PBC patients who were exposed to 10 mg seladelpar for ≥ 26 weeks (6.5 months) is 379, which is within the recommended sized cohort of exposed subjects according to the ICH guideline. In addition, 314 PBC patients were exposed to 10 mg seladelpar for ≥ 52 weeks. Thus, the safety database is considered to be of sufficient size to support the current marketing authorisation application of seladelpar for PBC.

Long-term exposure

Interim results as of 31 January 2024 were presented from supportive uncontrolled long-term study CB8025-31731-RE, where a total of 124 subjects had continuous exposure to seladelpar 10 mg for at least 2 years. This included 28 subjects who had received seladelpar in CB8025-32048 and continued treatment in CB8025-31731-RE, 6 of which had received treatment for 3 years, and 96 subjects who received seladelpar 10 mg for ≥ 2 years in the Legacy and CB8025-21838 parent study group, 24 of which had received treatment for 3 years.

Acknowledging that placebo-controlled study data on long-term safety of seladelpar exposure for more than one year in PBC patients is still missing, Long-term safety has been added to the Summary of Safety Concerns in the RMP as a category of Missing information. As recommended in '*Reflection paper on regulatory requirements for the development of medicinal products for primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), 4 December 2023*', a study duration is anticipated to be approximately 2 years, and for the demonstration of the long-term clinical outcomes a study duration of several years is anticipated. This is currently being evaluated in the ongoing open label extension study CB8025-31731-RE and the initiated controlled study CB8025-41837 (AFFIRM) with a fixed 3-year treatment duration.

2.6.8.2. Adverse events

The overall incidence of treatment-emergent adverse events (TEAEs) by treatment group is presented in *Table 40* below for placebo-controlled pivotal study CB8025-32048 and supportive CB8025-31735.

In the pivotal study CB8025-32048, 166 (86.0%) subjects experienced at least 1 TEAE. The incidence of TEAEs was similar between the seladelpar 10 mg group 111 (86.7%) and the placebo group 55 (84.6%).

In **supportive study CB8025-31735** with shorter treatment duration, the overall incidence of TEAEs was similar in the seladelpar 10 mg and 5 mg groups (65.2% and 62.9%, respectively) compared with the placebo group (73.6%).

Treatment-related TEAEs were somewhat more frequent in the seladelpar group of the pivotal study CB8025-32048, with 22 (17.2%) patients vs 8 (12.3%) in the placebo group. For study CB8025-31735, numbers were similar between the 10 mg seladelpar group of 15 (16.9%) vs 16 (18.4%) in the placebo group.

Approximately 90% of the TEAEs were mild to moderate, with no treatment-related Grade ≥ 3 TEAE.

Table 40: Overall summary of treatment-emergent adverse events (CB8025-32048, safety analysis set; CB8025-31735 safety set)

TEAE Category	CB8025-32048		CB8025-31735			
	Placebo (N=65) n (%)	**Seladelpar 10 mg (N=128) n (%)**	**Placebo (N=87) n (%)**	**Seladelpar 5 mg (N=89) n (%)**	**Seladelpar 10 mg (N=89) n (%)**	**All Seladelpar (N=178) n (%)**
Subjects with ≥ 1 TEAE	55 (84.6)	111 (86.7)	64 (73.6)	56 (62.9)	58 (65.2)	114 (64.0)
Treatment-emergent SAE	4 (6.2)	9 (7.0)	3 (3.4)	3 (3.4)	1 (1.1)	4 (2.2)
Grade ≥ 3 TEAE	5 (7.7)	14 (10.9)	6 (6.9)	3 (3.4)	5 (5.6)	8 (4.5)
Treatment-related TEAE	8 (12.3)	22 (17.2)	16 (18.4)	25 (28.1)	15 (16.9)	40 (22.5)
Treatment-related treatment-emergent SAE	0	0	0	0	0	0

Treatment-related Grade ≥ 3 TEAE	0	0	0	0	0	0
TEAE with action taken as permanent withdrawal of study drug	3 (4.6)	4 (3.1)	2 (2.3)	2 (2.2)	2 (2.2)	4 (2.2)
Treatment-related TEAE with action taken as permanent withdrawal of study drug	0	2 (1.6)	2 (2.3)	1 (1.1)	1 (1.1)	2 (1.1)
TEAE leading to study discontinuation	3 (4.6)	3 (2.3)	0	0	2 (2.2)	2 (1.1)
Treatment-related TEAE leading to study discontinuation	0	2 (1.6)	0	0	1 (1.1)	1 (0.6)
TEAE with fatal outcome	0	0	0	0	0	0

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event
Note: Adverse events in study CB8025-32048 were graded using Medical Dictionary for Regulatory Activities version 24.0. Adverse events in study CB8025-31735 were graded using Medical Dictionary for Regulatory Activities version 21.0.
Source: CB8025-32048 CSR Table 14.3.1.1.1, CB8025-31735 CSR Table 14.3.1.1. [Table 2.7.4-13]

Long-term safety

For the uncontrolled long-term study CB8025-31731-RE, interim results as of 31 January 2024 showed that overall, 27/28 (96.4%) of subjects in the CB8025-32048 continuous seladelpar group and 78/96 (81.3%) subjects in the Legacy and CB8025-21838 parent group reported at least 1 TEAE at some point during 3 years continuous treatment, with percentage numbers decreasing with each year (24 (85.7%) year 1, 22 (78.6%) year 2, and 6 (21.4%) year 3 for rollovers from CB8025-32048, 70 (72.9%) year 1, 55 (57.3%) year 2, and 24 (25.0%) year 3 for Legacy and CB8025-21838 Group). It is reassuring that continuous exposure to seladelpar 10 mg does not appear to cause an increase in number of TEAEs with increasing length of treatment, but rather a decrease, although with no placebo control group and small numbers of subjects (n=30) having received continuous treatment for 3 years.

2.6.8.2.1. Common TEAEs

Common TEAEs (defined by the applicant as those that occurred in ≥ 5% of subjects in either treatment group) of pivotal study CB8025-32048 and supportive study CB8025-31735 are presented by PT in the table below.

The highest TEAE incidences (≥ 5% difference) in pivotal study CB8025-32048 in the seladelpar treatment group compared with placebo were observed in the SOCs of injury, poisoning, and procedural complications (13.3% vs 6.2%, falls (2.3% vs 0%) and different kinds of fractures), and blood and lymphatic system disorders (11.7% vs 4.6%, PTs anaemia (4.7% vs. 3.1%), iron deficiency

anaemia (3.1% vs. 0)). Common TEAEs by PT that occurred at a higher incidence in the seladelpar arm relative to the placebo arm were COVID-19 (18.0% vs 15.4%), headache (7.8% vs 3.1%), abdominal pain (7.0% vs 1.5%), nausea (6.3% vs 4.6%), and abdominal distension (6.3% vs 3.1%).

Table 41: Most common treatment-emergent adverse events (≥ 5% of subjects) by preferred term (CB8025-32048, safety analysis set; CB8025-31735 safety set)

Preferred Term	CB8025-32048		CB8025-31735			
	Placebo (N=65) n (%)	Seladelpar 10 mg (N=128) n (%)	Placebo (N=87) n (%)	Seladelpar 5 mg (N=89) n (%)	Seladelpar 10 mg (N=89) n (%)	All Seladelpar (N=178) n (%)
Subjects with ≥ 1 TEAE	55 (84.6)	111 (86.7)	64 (73.6)	56 (62.9)	58 (65.2)	114 (64.0)
COVID-19	10 (15.4)	23 (18.0)	0	0	0	0
Headache	2 (3.1)	10 (7.8)	1 (1.1)	5 (5.6)	7 (7.9)	12 (6.7)
Abdominal pain	1 (1.5)	9 (7.0)	1 (1.1)	1 (1.1)	2 (2.2)	3 (1.7)
Arthralgia	4 (6.2)	8 (6.3)	5 (5.7)	5 (5.6)	4 (4.5)	9 (5.1)
Fatigue	4 (6.2)	8 (6.3)	8 (9.2)	2 (2.2)	4 (4.5)	6 (3.4)
Nausea	3 (4.6)	8 (6.3)	4 (4.6)	5 (5.6)	7 (7.9)	12 (6.7)
Abdominal distension	2 (3.1)	8 (6.3)	3 (3.4)	1 (1.1)	3 (3.4)	4 (2.2)
Nasopharyngitis	5 (7.7)	7 (5.5)	2 (2.3)	3 (3.4)	2 (2.2)	5 (2.8)
Pruritus	10 (15.4)	6 (4.7)	11 (12.6)	3 (3.4)	10 (11.2)	13 (7.3)
Asthenia	4 (6.2)	5 (3.9)	0	0	3 (3.4)	3 (1.7)
Pharyngitis	5 (7.7)	4 (3.1)	0	0	2 (2.2)	2 (1.1)
Urinary tract infection	4 (6.2)	4 (3.1)	0	2 (2.2)	5 (5.6)	7 (3.9)
Hypertension	4 (6.2)	4 (3.1)	0	1 (1.1)	2 (2.2)	3 (1.7)
Abdominal pain upper	3 (4.6)	3 (2.3)	3 (3.4)	8 (9.0)	6 (6.7)	14 (7.9)
Upper respiratory tract infection	6 (9.2)	1 (0.8)	2 (2.3)	6 (6.7)	4 (4.5)	10 (5.6)
Vertigo positional	4 (6.2)	1 (0.8)	0	0	0	0

Abbreviations: COVID-19 = coronavirus 2019; TEAE = treatment-emergent adverse event
Notes: A treatment-emergent adverse event (TEAE) is defined as any AE that starts after initiation of the study drug until up to 30 days after the last study drug administration.
A subject was counted only once for multiple events with the same preferred term.
Adverse events in study CB8025-32048 were graded using Medical Dictionary for Regulatory Activities version 24.0. Adverse events in study CB8025-31735 were graded using Medical Dictionary for Regulatory Activities version 21.0.
Source: CB8025-32048 CSR Table 14.3.1.2, CB8025-31735 CSR Table 14.3.1.2 [Table 2.7.4-14]

Exposure-adjusted analyses of TEAEs

The exposure-adjusted subject incidence of TEAEs in the pooled seladelpar 10 mg group (placebo-controlled and uncontrolled) was 55.39 per 100 subject-years compared to 132.33 per 100 subject-years in the placebo group. For treatment-related TEAEs, the numbers were 19.05 vs 27.80. Both of these categories indicate that seladelpar could reduce the numbers of TEAEs relative to placebo.

Subject incidence of TEAEs of interest, when adjusted for exposure, were similar between placebo, seladelpar 10 mg, and seladelpar ≤ 10 mg for muscle-related, renal-related, pancreatic-related, and cardiovascular related TEAEs. The exposure-adjusted subject incidence of pruritus-related TEAEs and

liver-related TEAEs were lower in subjects treated with seladelpar 10 mg and subjects treated with seladelpar ≤ 10 mg compared to the placebo group.

2.6.8.2.2. Adverse drug reactions

In pivotal study CB8025-32048, TEAEs assessed as treatment-related by the Investigator were reported in 22 (17.2%) of subjects in the seladelpar 10 mg group and 8 (12.3%) of subjects in the placebo group. The most common treatment-related TEAEs reported for ≥ 2 subjects by PT in the seladelpar arm 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%). The only treatment-related TEAE reported for ≥ 2 subjects by PT in the placebo arm was dry mouth (3.1%). Treatment-related TEAEs of liver function test increased as assessed by the Investigator were infrequent and reported for 1 subject in each arm (seladelpar 0.8%; placebo 1.5%).

In supportive study CB8025-31735, TEAEs assessed as treatment-related by the Investigator were reported in 16.9% of subjects in the seladelpar 10 mg group and 18.4% of subjects in the placebo group. The most common (≥ 2 subjects) treatment-related TEAEs in the seladelpar 10 mg group were pruritus (3.4%), and nausea, abdominal pain upper, diarrhoea, gastroesophageal reflux disease, asthenia, and headache (2.2% each). Treatment-related TEAEs that occurred at a ≥ 2% higher incidence in the seladelpar 10 mg group compared with the placebo group were dry mouth (3.4% vs 0%) and abdominal pain upper, diarrhoea, gastroesophageal reflex disease, headache, weight increased, dry eye, and renal impairment (2.2% vs 0% each).

No summary table was presented of treatment-related TEAEs by SOC for either of the two phase 3 trials, but several of the PTs with highest frequency was from the SOC Gastrointestinal disorders. In study CB8025-32048, 9 (7.0%) in the seladelpar group had treatment-related TEAE in SOC Gastrointestinal disorders, vs. 3 subjects (4.6%) in the placebo group. For study CB8025-31735, the numbers were 9 (10.1%) in seladelpar 10 mg and 4 (4.6%) in placebo.

There were not many details specified in the respective CSRs on how the relatedness between the TEAE and the treatment was determined. It appears to have been the decision of each investigator alone (reported as "possible", "probably", or "definite").

Adverse drug reactions in SmPC

The most common TEAEs by PT reported in the pivotal study CB8025-32048, occurring in ≥ 5% of subjects in the seladelpar arm and at an incidence of ≥ 1% higher than in the placebo arm were Headache, Nausea, Abdominal pain, and Abdominal distension. These were accepted to be included in section 4.8 of the SmPC based on a numerical imbalance of events in seladelpar versus placebo groups.

Further analysis of pooled data from both the pivotal study CB8025-32048 and supportive study CB8025-31735, 3 TEAEs were reported at least 2 times higher in the seladelpar group than the placebo group, two already accepted ADRs Headache, Abdominal pain and in addition Dizziness. Similarly, analysis of treatment-related TEAEs as investigator assessed from pooled data resulted in already accepted ADR Headache and in addition Diarrhoea. These potential ADRs were then evaluated further for a possible causal association.

Dizziness

All 9 events (occurring in 9 subjects) of dizziness reported in seladelpar group were non-serious and none led to study drug discontinuation. The median time to onset of the event was 40.5 days (range: 1 to 298 days). For 8 out of 9 events of dizziness there were alternative explanations including use of concomitant medications associated with dizziness and/or medical history (vertigo, vestibular disorder, bradycardia, anaemia, hypertension). There was a similar frequency of unique subjects in the seladelpar group (4.2%) versus placebo group (3.9%) reporting any event of dizziness, vertigo, vertigo positional, or presyncope. Additionally, there was no imbalance noted for ear and labyrinth disorders. Overall, there was insufficient evidence to suggest a causal association with dizziness, or similar PTs.

Diarrhoea

All events of diarrhoea regardless of investigator assessed causality were reviewed, revealing no difference in frequency of diarrhoea reported in the seladelpar group (4.6%) versus placebo group (4.6%). All 16 events (occurring in 14 subjects) of diarrhoea reported in the seladelpar group were non-serious and none led to study drug discontinuation. The median time to onset for the event was 26 days (range: 2 to 343 days) with no particular pattern observed, with a median duration of 5 days. 9 out of the 16 events of diarrhoea had plausible alternative explanations noted, including use of concomitant medications associated with diarrhoea and/or medical history. For the remaining 7 events without any clear alternative explanations, the diarrhoea resolved despite no action taken with seladelpar. Overall, there was insufficient evidence to suggest a causal association with diarrhoea.

Frequencies

Frequencies of the adverse drug reactions in section 4.8 were based on pooled data from pivotal study CB8025-32048 and supportive study CB8025-31735. Abdominal pain, along with similar PTs of abdominal pain upper, abdominal discomfort, and abdominal pain lower, were pooled together.

This resulted in the following table for section 4.8 of the SmPC:

System Organ Class	Very Common	Common
Nervous System Disorders		Headache
Gastrointestinal Disorders	Abdominal pain[a]	Nausea Abdominal distension

Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort

2.6.8.3. Serious adverse event/deaths/other significant events

2.6.8.3.1. AEs of special interest

Adverse events of interest across the seladelpar development programme were those events potentially reflecting liver, muscle, renal, and pancreatic safety. Other adverse events of interest included cardiovascular events and adverse events associated with pruritus. These events were defined differently across the seladelpar development programme (predefined search strategy for each category for CB8025-32048; broader SOC categories for CB8025-31735) and are presented here by event type to summarise key aspects of safety events. Comparison is limited by the use of different search strategies and duration of follow-up.

Table 42: Overall summary of treatment-emergent adverse events of interest (CB8025-32048, safety analysis set and CB8025-31735 safety set)

TEAE Category	CB8025-32048		CB8025-31735			
	Placebo (N = 65) n (%)	Seladelpar 10 mg (N = 128) n (%)	Placebo (N = 87) n (%)	Seladelpar 5 mg (N = 89) n (%)	Seladelpar 10 mg (N = 89) n (%)	All Seladelpar (N = 178) n (%)
Subjects with at least one:						
Liver-related TEAEs	6 (9.2)	8 (6.3)	3 (3.4)	3 (3.4)	3 (3.4)	6 (3.4)
Muscle-related TEAEs	5 (7.7)	8 (6.3)	12 (13.8)	15 (16.9)	15 (16.9)	30 (16.9)
Renal-related TEAEs	0	0	1 (1.1)	5 (5.6)	3 (3.4)	8 (4.5)
Pancreatic-related TEAEs	1 (1.5)	2 (1.6)	0	1 (1.1%)	1 (1.1%)	2 (1.1%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA queries; SOC = system organ class; TEAE = treatment-emergent adverse event
Source: CB8025-32048 CSR Table 14.3.1.10.1, Table 14.3.1.11.1, Table 14.3.1.12.1, and Table 14.3.1.13.1; CB8025-31735 CSR Table 14.3.1.2 [Table 2.7.4-17]

Liver related TEAEs

In phase 2 study CB8025-21528 examining 50 mg and 200 mg doses of seladelpar, 3 subjects discontinued treatment due to AEs associated with Grade 3 liver transaminase elevations. Subsequently, comprehensive safety monitoring criteria were established for monitoring of liver events during all seladelpar PBC studies.

The totality of liver-related TEAEs in the pivotal study CB8025-32048 are summarised in the table below. There were few cases recorded, a lower percentage of subjects in the seladelpar group than in the placebo group experienced at least 1 liver-related TEAE. The PTs included in this TEAE category were individually reported in each arm with the exception of Hepatic cirrhosis. A slightly higher percentage of subjects in the seladelpar group, 3 subjects (2.3%), than in the placebo group, 1 subject (1.5%), experienced hepatic cirrhosis, which were not treatment-related per the Investigator assessment.

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.

Liver-related TEAEs assessed by the Investigator as treatment-related 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 study drug were reported for 1 subject in the seladelpar group (liver function test increased) and 1 subject in the placebo group (hyperbilirubinaemia).

Table 43: Treatment-emergent adverse events potentially reflecting liver-related toxicity by preferred term (CB8025-32048, safety analysis set)

Preferred Term	**Placebo (N = 65) n (%)**	**Seladelpar 10 mg (N = 128) n (%)**
Subjects with ≥ 1 liver-related TEAE	6 (9.2)	8 (6.3)
Hepatic cirrhosis	1 (1.5)	3 (2.3)
Blood bilirubin increased	1 (1.5)	1 (0.8)*
Liver function test increased	1 (1.5)*, **	1 (0.8)*, **
Ascites	0	1 (0.8)
Drug-induced liver injury	0	1 (0.8)
Hepatic lesion	0	1 (0.8)
Hepatomegaly	0	1 (0.8)
Oesophageal varices haemorrhage	0	1 (0.8)
Hyperbilirubinaemia	1 (1.5)**	0
Nonalcoholic fatty liver disease	1 (1.5)	0
Portal hypertensive gastropathy	1 (1.5)	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event. *Assessed as treatment-related per the Investigator assessment. ** TEAE leading to discontinuation of study drug.
Source: CB8025-32048 CSR Table 14.3.1.11.1 [Table 2.7.4-18]

Muscle-related TEAEs

Incidences for muscle-related TEAE in pivotal study CB8025-32048 were fairly frequent but overall similar between the treatment groups (seladelpar 8 (6.3%) vs. placebo 5 (7.7%)). One Grade 3 event of myalgia was reported in the placebo group, whereas all events occurring in the seladelpar group were mild to moderate. There were no events associated with notable CK increases related to seladelpar.

In supportive study CB8025-31735, higher incidences of muscle-related TEAEs were reported for both placebo and seladelpar groups than in pivotal study CB8025-32048, even though the study was shorter. However, in study CB8025-31735, adverse events of interest were summarised using SOC categories, thus including a broader array of terms.

Overall, the reported muscle-related TEAEs in study CB8025-32048 and CB8025-31735 revealed no safety concerns.

Renal-related TEAEs

There were no renal-related TEAEs reported in pivotal study CB8025-32048.

In supportive study CB8025-31735, there was an imbalance in TEAEs in the Renal and Urinary Disorders SOC, 1 subject (1.1%) treated with placebo, 5 subjects (5.6%) treated with seladelpar 5 mg, and 3 subjects (3.4%) treated with seladelpar 10 mg. Numbers are however quite small.

TEAEs related to pancreatic toxicity, pruritus and cardio-vascular diseases.

TEAEs potentially reflecting pancreatic-related toxicity were infrequent in the study population but occurred in a similar percentage of subjects in the seladelpar and placebo arms (1.6% vs. 1.5%).

Generally, a lower incidence of pruritus TEAEs was reported in the seladelpar groups compared with the placebo groups. See further in the Efficacy evaluation.

Incidence for cardiovascular-related TEAE in study CB8025-32048 was slightly elevated in the seladelpar group with 13 subjects (10.2%) vs. 5 (7.7%) in the placebo group. Most PTs were individually reported in each treatment arm with the exception of blood creatine phosphokinase increased, oedema peripheral, and palpitations reported for 2 subjects each in the seladelpar arm. One event in this category was assessed as treatment-related by the Investigator, which was a mild Grade 1 TEAE of CK increased reported in the placebo arm. Overall, the reported cardiovascular-related TEAEs revealed no safety concerns.

2.6.8.3.2. Serious Adverse Events and deaths

Treatment-emergent SAEs tended to be reported in similar rates in subjects in the treatment groups and the placebo groups across the clinical studies. In pivotal study CB8025-32048, treatment-emergent SAEs were reported in 9 (7.0%) of subjects in the seladelpar 10 mg group and 4 (6.2%) of subjects in the placebo group. All SAEs were individually reported with the exception of COVID-19, which occurred in 1 subject in each arm. None of the treatment-emergent SAEs were assessed as treatment-related by the Investigator.

None of the treatment-emergent SAEs in study CB8025-31735 or CB8025-31731-RE were assessed as treatment-related by the Investigator and none were reported in > 1 subject each.

Overall, the SAEs revealed no safety concerns.

There were no deaths during participation reported in either controlled or uncontrolled studies. A late-breaking treatment-emergent SAE leading to death was reported in the initial MA submission after the data cutoff date in study CB8025-31731-RE. The fatal event was considered unlikely related to study drug.

Table 44: Serious treatment-emergent adverse events by preferred term (CB8025-32048, safety analysis set; CB8025-31735 safety set)

Preferred Term	CB8025-32048		CB8025-31735			
	Placebo (N=65) n (%)	Seladelpar 10 mg (N=128) n (%)	Placebo (N=87) n (%)	Seladelpar 5 mg (N=89) n (%)	Seladelpar 10 mg (N=89) n (%)	All Seladelpar (N=178) n (%)
Subjects with ≥ 1 treatment-emergent SAE	4 (6.2)	9 (7.0)	3 (3.4)	3 (3.4)	1 (1.1)	4 (2.2)
COVID-19	1 (1.5)	1 (0.8)	0	0	0	0
Acute respiratory failure	0	1 (0.8)	0	0	0	0
COPD	0	1 (0.8)	0	0	0	0
Coagulopathy	0	1 (0.8)	0	0	0	0
Coronary artery disease	0	1 (0.8)	0	0	0	0
Duodenal obstruction	0	1 (0.8)	0	0	0	0
Dyspnoea exertional	0	1 (0.8)	0	0	0	0
Femur fracture	0	1 (0.8)	0	0	0	0

Invasive ductal breast carcinoma	0	1 (0.8)	0	0	0	0
Oesophageal varices haemorrhage	0	1 (0.8)	0	0	0	0
Papillary thyroid cancer	0	1 (0.8)	0	0	0	0
Rotator cuff syndrome	0	1 (0.8)	0	0	0	0
Bladder cancer	1 (1.5)	0	0	0	0	0
Headache	1 (1.5)	0	0	0	0	0
Pneumonia	1 (1.5)	0	0	0	0	0
Presyncope	1 (1.5)	0	0	0	0	0
Suicide attempt	1 (1.5)	0	0	0	0	0
Cellulitis	0	0	0	0	1 (1.1)	1 (0.6)
Pyelonephritis acute	0	0	1 (1.1)	0	0	0
Cognitive disorder	0	0	0	1 (1.1)	0	1 (0.6)
Partial seizures	0	0	1 (1.1)	0	0	0
Leukocytosis	0	0	0	1 (1.1)	0	1 (0.6)
Adenoid cystic carcinoma	0	0	0	1 (1.1)	0	1 (0.6)
Rectal polyp	0	0	1 (1.1)	0	0	0

Abbreviations: COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus 2019; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Notes: A subject was counted only once for multiple events with the same preferred term.
Adverse events were graded using Medical Dictionary for Regulatory Activities version 24.0. Adverse events in study CB8025-31735 were graded using Medical Dictionary for Regulatory Activities version 21.0.
Source: CB8025-32048 CSR Table 14.3.2.1.2, CB8025-31735 CSR Table 14.3.2.1 [Table 2.7.4-15]

Malignancies

Based on non-clinical rodent carcinogenicity data, concerns were raised for malignancies developing with seladelpar treatment. However, most tumours seen in animal models were not considered relevant for humans (please refer to non-clinical assessment).

Data on malignancies from the full clinical programme was presented and discussed in light of the non-clinical concerns. The data on observed malignancies from the clinical studies showed a cluster of skin related malignancies (basal cell carcinoma (n=4), squamous cell carcinoma (n=4), and squamous cell carcinoma of skin (n=3)) that was not reflected in the placebo group. However, malignancies were only reported for subjects receiving placebo during the 1 year they were included in the controlled study, where subjects sum of exposure in years was 89.9 years. For patients treated with seladelpar 10 mg subjects sum of exposure was 865.1 years. These groups are thus not entirely comparable. In addition, numbers on incidence of skin related malignancies in the population presented from the literature was similar to what was found in the clinical studies. Thus, malignancies in humans are not considered to be a potential risk at this time but should continue to be monitored in the ongoing clinical studies. Malignancies tend to take time to develop but are very severe adverse events.

Table 45: Exposure-adjusted malignancy (FMQ) TEAEs by preferred term – all exposure (seladelpar ≤ 10 mg) pool group (safety analysis set)

Preferred Term	Placebo (N = 152) (E = 89.9 years) n (n/E)	Any Seladelpar 10 mg (N = 486) (E = 865.1 years) n (n/E)	Any Seladelpar (N = 540) (E = 883.2 years) n (n/E)
Subjects with At Least One TEAE	2 (0.0222)	17 (0.0197)	18 (0.0204)
Basal cell carcinoma	0	4 (0.0046)	4 (0.0045)
Squamous cell carcinoma	0	4 (0.0046)	4 (0.0045)
Squamous cell carcinoma of skin	0	3 (0.0035)	3 (0.0034)
Adenocarcinoma of the cervix	0	1 (0.0012)	1 (0.0011)
Chronic myeloid leukaemia	0	1 (0.0012)	1 (0.0011)
Intraductal papillary mucinous neoplasm	0	1 (0.0012)	1 (0.0011)
Invasive ductal breast carcinoma	0	1 (0.0012)	1 (0.0011)
Lymphoma	0	1 (0.0012)	1 (0.0011)
Malignant neoplasm of unknown primary site	0	1 (0.0012)	1 (0.0011)
Papillary thyroid cancer	0	1 (0.0012)	1 (0.0011)
Precancerous cells present	0	1 (0.0012)	1 (0.0011)
Precancerous skin lesion	0	1 (0.0012)	1 (0.0011)
Adenoid cystic carcinoma	0	0	1 (0.0011)
Bladder cancer	1 (0.0111)	0	0
Breast cancer	1 (0.0111)	0	0

E = subjects sum of exposure in years; FMQ = FDA Medical Queries; N = total number of subjects; n = number of subjects in the category; TEAE = treatment-emergent adverse event
FMQ search terms for malignancy are provided in the appendix.
Adverse events were graded using MedDRA Version 24.0 and FMQ Version 2.1.
Data cutoff date: 31 January 2024.
Exposure rate (n/E) is calculated as the number of subjects with TEAEs divided by total exposure years.
Adverse events are sorted by descending frequency of preferred term in the Any Seladelpar 10 mg group, then the Any Seladelpar group, then Placebo.
The following studies are included: CB8025-32048, CB8025-31735, CB8025-21629, CB8025-31731, CB8025-21838 and CB8025-31731-RE (all seladelpar treatment subjects data are included).
Treatment groups:
Placebo: Subjects who were treated with placebo in placebo-controlled PBC studies.
Any Seladelpar 10 mg: All subjects (in placebo-controlled and uncontrolled PBC studies) who were treated with 10 mg seladelpar.
Any Seladelpar: All subjects who were treated with any dose of seladelpar ≤10 mg in all PBC studies (placebo-controlled and uncontrolled).
Source: EU-Q91 Table 15

2.6.8.4. Laboratory findings

Additional safety monitoring criteria

Additional safety monitoring criteria were implemented in the design of later studies and guidance to Investigators were outlined for laboratory findings and clinical symptoms potentially concerning for liver, muscle, renal, or pancreatic toxicity. For subjects who met prespecified criteria for laboratory and

clinical findings, Investigators were instructed to decrease, interrupt, or discontinue study drug, depending on findings during treatment and follow-up testing.

Biochemistry laboratory parameters assessed for muscle or pancreatic toxicity did not raise any safety concerns. Nor did the histopathological evaluation of 64 paired liver biopsy tissues from the from pivotal study CB8025-32048 and long-term study CB8025-31731-RE. Mean values and percent changes in haematology parameters from baseline were generally similar between the seladelpar and placebo arms. There were no clinically meaningful changes in vital signs parameters in either treatment arm. There were no concerning observations for cardiac safety, and no QTc prolongation in a TQT study (10 mg and 200 mg, CB8025-11733).

Mean values and percent changes in haematology parameters from baseline were generally similar between the seladelpar and placebo arms. A search of the pooled safety analysis data set for studies CB8025-32048 and CB8025-31735 using the anaemia FMQ identified a total of 14 subjects with at least 1 event of anaemia (total of 15 events) including 12 seladelpar-treated subjects (3.9%) and 2 placebo-treated subjects (1.3%). As most of the haemoglobin changes were grade 1 and anaemia appears to represent a comorbidity in the PBC patient population, no causal link between seladelpar and anaemia could be established.

2.6.8.4.1. Liver function

In the phase 2 study CB8025-21528, 13 patients were exposed to 50 mg seladelpar and 12 PBC patients were exposed to 200 mg seladelpar, 13 patients received placebo. Median duration of exposure to seladelpar was 44.0, 31.0, and 21.0 days in the placebo and seladelpar 50 and 200 mg groups, respectively, and ranged from 1 to 91 days. The study was terminated early when 3 subjects had experienced a Grade 3 ALT elevation that were attributed to study drug; 1 subject received 50 mg and 2 received 200 mg. The transaminases elevations were rapid (within 2 weeks of treatment initiation), asymptomatic, not associated with an abnormal increase in bilirubin, and fully reversible upon study drug discontinuation. Information on the study results was included in section 4.9 of the SmPC.

In pivotal study CB8025-32048, for liver biochemistry laboratory parameters of interest, fewer subjects treated with seladelpar than subjects who received placebo met the criteria in at least 1 category (11 (8.6%) vs. 10 (15.4%)). 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. On an individual level, CTCAE grade 2 shifts from baseline were noted for AST and ALT in 2 respectively 3 subjects in the seladelpar group compared to none in the placebo group. Three potential Hy's law cases were identified using an eDISH plot, but none of them were considered to be DILI.

In supportive study CB8025-31735, shifts from normal to high postbaseline ALT, AST, and total bilirubin values were observed in a small number of subjects and worsened by no more than 2 grades across all groups. The frequency of shifts from normal to high in ALT, AST, and total bilirubin were similar in placebo, seladelpar 5 mg, and seladelpar 10 mg groups.

Information on monitoring of liver test abnormalities and subsequent treatment adjustments is included in SmPC section 4.4. The risk for hepatotoxicity is also reflected in the RMP as an important potential risk.

2.6.8.4.2. Renal function

In phase 2 study CB8025-21528 which evaluated seladelpar doses higher than 10 mg, a dose-dependent increase in serum creatinine was observed (serum creatinine changes were 2.7%, 14.08%, and 27.36% for the placebo, seladelpar 50 mg, and seladelpar 200 mg groups, respectively). For 1 subject (seladelpar 200 mg) in whom a serum creatinine elevation led to an AE of acute kidney injury, creatinine returned to baseline upon treatment discontinuation. Seladelpar was associated with dose-dependent elevations in serum creatinine (mean percent increases from baseline to Week 12 of 1.89% and 23.47% in the seladelpar 50 mg and 200 mg groups, respectively) in this study. Information on dose dependent increases in serum creatinine was included in section 4.9 of the SmPC.

In pivotal study CB8025-32048, seladelpar was associated with an increase in the subject incidence of renal safety laboratory parameters of interest (12 (9.4%) subjects in the seladelpar 10 mg arm; 1 (1.5%) subject in the placebo arm). All of these subjects met criteria for eGFR decrease ≥ 25% from baseline, and 1 subject in the seladelpar 10 mg arm also met criteria for creatinine increase ≥ 1.5× baseline. All subjects with decreases in eGFR had proportional increases in creatinine, consistent with the creatinine-based eGFR formula. Median increases in the creatinine values from baseline of up to 6.6% were observed with the 10 mg dose compared with up to 2.2% in subjects taking placebo. In the seladelpar group, most of the subjects (9/12 [75%]) had resolution at the next study visit without change in study drug. There was no observed pattern of timing of onset. Overall, changes were mild and there were no associated TEAEs.

In supportive study CB8025-31735, mean serum creatinine values remained within normal ranges for all treatment groups. At Month 6, percent change from baseline in creatinine was 9.1% for placebo and 12.28% for seladelpar 10 mg. Shifts in eGFR from normal (≥ 60 mL/min/1.73m^2) to low (≥ 30 to < 60 mL/min/1.73m^2) were observed in 9% of subjects in the seladelpar 10 mg group compared with 4.6% of the placebo group.

A mechanism for increased levels of creatinine has not been established, but it has been proposed that rather than a decline in renal function, PPARα and mixed PPARα/δ agonists increase the metabolic production rate of creatinine independent of muscle cell lysis, or a decrease in creatinine clearance without a change in glomerular filtration rate. Alternative mechanisms possible for seladelpar include increased creatinine production resulting from non-enzymatic conversion of creatine to creatinine (seladelpar increased production of creatinine by about 2.3-fold in Cynomolgus monkeys fed a western diet), increased production of creatinine as a result of improved liver function, or OAT3 inhibition in the kidney by the metabolite M3. Post-hoc analyses using an alternative cystatin C-based equation to calculate eGFR further supported that changes were not reflective of a true decline in renal function.

Based on the above, information on dose dependent increases in serum creatinine as observed in the pivotal study should be reflected in the SmPC section 4.4. There is no apparent risk for kidney injuries from the studies presented, but to avoid unnecessary interruptions of seladelpar treatment due to perceived reduction in eGFR and kidney function with increases in creatinine probably due to causes other than kidney injuries, this information is considered valuable to the prescriber (SmPC comment).

2.6.8.5. *In vitro biomarker test for patient selection for safety*

No *in vitro* biomarker test for patient selection for safety was used.

2.6.8.6. Safety in special populations

There were no pregnant subjects and no subjects with hepatic impairment CP-B or C in the pivotal study CB8025-32048. Only one subject, in the active treatment group, had renal impairment and

reported no SAEs or AEs leading to discontinuation. No other relevant special populations were reported.

2.6.8.6.1. Subjects with hepatic impairment

The target population of this medicinal product is to a large extent expected to have (or subsequently develop) an impaired hepatic function. Thus, clinical consequences of any hepatic injuries from the active substance would likely be more critical in these patients. Seladelpar seems to be mainly eliminated via metabolism. This in combination with signals regarding hepatic safety with higher doses of seladelpar from previous studies leads to an extra requirement for the characterisation of safety in individuals with impaired hepatic function.

Safety of seladelpar in subjects with cirrhosis and varying degrees of hepatic impairment was assessed in 2 phase 1 studies (CB8025-11732 and CB8025-21838, see Pharmacokinetics Section Special populations). In general, exposure to seladelpar increased with increasing hepatic impairment, but no safety concerns were identified during dosing of limited duration (≤ 28 days). The final cohort of PBC patients with Child-Pugh C of ongoing phase 1 hepatic impairment study CB8025-21838 remains to be completed, but for the 4 subjects who received a single dose of seladelpar 10 mg, the safety profile was comparable with that of other subjects in the study.

In pivotal study CB8025-32048, a total of 27 (14%) subjects (14.1% and 13.8% of subjects in the seladelpar and placebo groups, respectively) had cirrhosis at baseline. Numerical differences in various TEAEs between the treatment groups were seen with generally higher numbers in the cirrhotic groups as could be expected with more severe disease, but few patients were included in the subgroup.

Table 46: Overall Summary of treatment-emergent adverse events of cirrhosis subpopulation (CB8025-32048, safety analysis set)

	Cirrhotic		**Non-cirrhotic**	
	Placebo (N = 9) n (%)	**Seladelpar 10 mg (N = 18) n (%)**	**Placebo (N = 56) n (%)**	**Seladelpar 10 mg (N = 110) n (%)**
Subjects with ≥ 1 TEAE	8 (88.9)	16 (88.9)	47 (83.9)	95 (86.4)
Treatment-emergent SAE	1 (11.1)	2 (11.1)	3 (5.4)	7 (6.4)
Grade ≥ 3 TEAE	2 (22.2)	2 (11.1)	3 (5.4)	12 (10.9)
Treatment-related TEAE	2 (22.2)	2 (11.1)	6 (10.7)	20 (18.2)
Treatment-related Treatment-emergent SAE	0	0	0	0
Treatment-related Grade ≥ 3 TEAE	0	0	0	0
TEAE with Fatal Outcome	0	0	0	0
TEAE with Action Taken as Permanent Withdrawal of Study Drug	2 (22.2)	0	1 (1.8)	4 (3.6)
Treatment-related TEAE with Action Taken as Permanent Withdrawal of Study Drug	0	0	0	2 (1.8)
TEAE Leading to Study Discontinuation	2 (22.2)	0	1 (1.8)	3 (2.7)
Treatment-related TEAE Leading to Study Discontinuation	0	0	0	2 (1.8)

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event
Note: Adverse events were graded using Medical Dictionary for Regulatory Activities version 24.0. Percentages are based on the number of subjects in the Safety Analysis Set under each treatment group for corresponding subgroup.

Source: CB8025-32048 CSR Table 14.3.1.1.8 [Table 2.7.4-28]

The uncontrolled long-term study CB8025-31731-RE included (as of 31 January 2024) 62 subjects with cirrhosis (nearly all with CP-A status), and 26 subjects with cirrhosis and suspected portal hypertension. Based on quite few subjects and for mild cirrhosis, the analyses presented indicated a safety profile that was overall similar to subjects with CP-A cirrhosis and the overall study population, and comparable between seladelpar 10 mg and placebo.

The subpopulation in pivotal study CB8025-32048 with total bilirubin > 1.0× ULN at baseline included a total of 25 (13.0%) subjects (20 (15.6%) and 5 (7.7%) in the seladelpar and placebo groups, respectively). Also, these subjects had a numerically greater number of TEAEs, treatment-emergent SAEs, and Grade ≥ 3 TEAEs compared with subjects with normal baseline total bilirubin in both the seladelpar and placebo groups, but subject incidence of these events was balanced between treatment groups, and the preferred terms were generally reflective of more advanced disease in this population.

Patients with elevated bilirubin at baseline who received 10 mg seladelpar and continued to uncontrolled long-term study CB8025-31731-RE comprised 52 subjects. Exposure-adjusted numbers for subjects with at least one TEAE tended to increase with each year of treatment (n (n/exposure in years): 19 (1.0) year 1, 16 (1.3) year 2, and 2 (2.0) year 3 for rollovers from CB8025-32048, 20 (0.8) year 1, 11 (0.8) year 2, and 3 (1.1) year 3 for Legacy and CB8025-21838 Group), but this is based on few patients, especially in the year 3 cohort (N = 5 for rollovers from CB8025-32048 and N = 7 for Legacy and CB8025-21838 group). It is however not surprising to see tendencies towards a slightly worsening safety profile for seladelpar in subjects with elevated TB, reflecting a population with slightly more severe disease.

In keeping with study entry criteria, nearly all subjects with cirrhosis in phase 2 or 3 studies had hepatic impairment CP-A. Thus, the safety of seladelpar in PBC subjects with moderate (CP-B) or severe (CP-C) hepatic impairment has not been established. This is currently reflected in SmPC section 4.2, that treatment discontinuation should be considered if the patient progresses to moderate hepatic impairment, and use is not recommended in patients with severe hepatic impairment.

PBC is a progressive disease and section 4.2 of the SmPC includes information on measures to take in case of disease progression to worse PBC or cirrhosis CP-B/C. Section 4.4 includes information on monitoring liver tests, and measures to take in case the patient develops signs and symptoms consistent with liver dysfunction.

In the SmPC, a warning on '*Biliary Obstruction*' in section 4.4 is proposed. If a medicine is partly or mainly excreted in the bile it is clinical practise to stop or reduce the dose during such an event.

2.6.8.6.2. Subjects with renal impairment

Overall, treatment with a single dose 10 mg seladelpar in subjects with normal renal function or with mild, moderate, or severe renal impairment showed comparable results across the treatment groups and no dose adjustment is required. Patients with end-stage renal disease on dialysis have not been studied, and use is not recommended in these patients. See section Pharmacokinetics above for more details.

2.6.8.6.3. Monotherapy

Few patients were included in pivotal study CB8025-32048 receiving seladelpar as monotherapy (8 subjects, 6.3% and 4 subjects, 6.2% in the seladelpar and placebo groups, respectively). In the

placebo group, i.e. patients with neither UDCA nor seladelpar treatment, 4 of 4 subjects (100.0%) experienced TEAEs, compared to 5 of 8 subjects (62.5%) in the seladelpar 10 mg monotherapy group. In the overall seladelpar population of this study, 111 (86.7%) subjects experienced ≥ 1 TEAE. Thus, although the monotherapy group had a too limited sample size to draw firm conclusions, the safety profile appears overall similar to that of subjects who received seladelpar in combination with UDCA.

2.6.8.6.4. Pregnancy and breast-feeding

Only two pregnancies have been documented, both in study CB8025-31731-RE: 1 subject elected to terminate the pregnancy and continue treatment, and the other subject discontinued treatment but remained on study as of the data cutoff date. This subject did not experience any AEs during the pregnancy. No cases of breast-feeding while on treatment have been reported. Low exposure is expected during pregnancy and even less during breast feeding.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity in clinically relevant exposure levels. However, the SmPC states that as a precautionary measure, it is preferable to avoid the use of seladelpar during pregnancy, and 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.

No safety concern for use in breast-feeding is identified. The lack of information from use in pregnancy is reflected in the RMP as Missing Information.

2.6.8.6.5. Age at screening

In the pivotal study CB8025-32048, age at screening was between 28-75 years. Only 41 subjects over 65 years were included of a total of 193, 29 (22.7%) in the seladelpar group and 12 (18.5%) in the placebo group. The incidence of overall TEAEs was 88.2% in subjects < 65 years and 78.0% in subjects ≥ 65 years. Total subjects with an AE were comparable between the seladelpar age groups below and above 65 years (86 (86.9%) vs 25 (86.2%)).

Among the subset of subjects ≥ 65 years, the incidences of TEAEs, treatment-emergent SAEs, and Grade ≥ 3 TEAEs were higher in the seladelpar 10 mg group compared with the placebo group, although the number of subjects in the placebo group was small. Among subjects who were ages 65-75 at study entry, the incidence of SAEs among subjects randomised to seladelpar was higher than among those randomised to placebo (5 (17.2%) vs 0 subjects). The PTs of the 8 SAEs in the 5 subjects were likely attributable to age and underlying medical conditions rather than seladelpar (Duodenal obstruction, Chronic obstructive pulmonary disease (verbatim term: COPD exacerbation), Invasive ductal carcinoma, Acute respiratory failure, Femur fracture, Coronary artery disease (verbatim term: Worsening coronary artery disease), Exertional dyspnoea, and Oesophageal varices haemorrhage).

Among subjects aged ≥65, the SOCs with events that occurred more frequently in subjects treated with seladelpar compared to those treated with placebo were Nervous system disorders (4 [13.8%] vs 1 [8.3%]), Accidents and injuries (6 [20.7%] vs 1 [8.3%]), Anticholinergic syndrome (3 [10.3%] vs 0), and Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures (8 [27.6%] vs 0). The majority of nervous system events (including dizziness) were confounded by use of concomitant medications and/or medical history. The difference in the SOC 'Accidents and Injuries and Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures' was likely secondary to the numerical imbalance in the PTs of Fall and various fracture events. The 3 fractures in seladelpar-treated subjects aged ≥65 occurred in the context of an imbalance in osteoporosis between the treatment groups, and 1 case of motor vehicle accident.

The safety profile among subjects aged ≥65 appeared overall similar to the younger population, with some numerical imbalances with certain categories occurring more frequently in subjects treated with seladelpar and certain categories of events occurring more frequently in placebo.

Table 47: Summary of Safety in Elderly Subjects in Study CB8025-32048

	Seladelpar 10 mg		**Placebo**	
MedDRA Terms[a]	**<65 N=99 n (%)**	**65-75 N=29 n (%)**	**<65 N=53 n (%)**	**65-75 N=12 n (%)**
Total subjects with an AE	86 (86.9)	25 (86.2)	48 (90.6)	7 (58.3)
Subjects with Serious AEs	4 (4.0)	5 (17.2)	4 (7.5)	0
- Fatal	0	0	0	0
- Hospitalisation/ prolong existing hospitalisation	3 (3.0)	4 (13.8)	2 (3.8)	0
- Life-threatening	0	0	1 (1.9)	0
- Disability/ incapacity	0	0	0	0
- Other (medically significant)	1 (1.0)	1 (3.4)	1 (1.9)	0
AE leading to drop-out	3 (3.0)	0	3 (5.7)	0
Psychiatric disorders	6 (6.1)	0 (0.0)	3 (5.7)	1 (8.3)
Nervous system disorders	18 (18.2)	4 (13.8)	8 (15.1)	1 (8.3)
Accidents and injuries	7 (7.1)	6 (20.7)	2 (3.8)	1 (8.3)
Cardiac disorders	3 (3.0)	2 (6.9)	2 (3.8)	1 (8.3)
Vascular disorders	6 (6.1)	2 (6.9)	4 (7.5)	1 (8.3)
Cerebrovascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	46 (46.5)	12 (41.4)	30 (56.6)	5 (41.7)
Anticholinergic syndrome	8 (8.1)	3 (10.3)	6 (11.3)	0 (0.0)
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	10 (10.1)	8 (27.6)	6 (11.3)	0 (0.0)
<other AE appearing more frequently in older subjects>	Not applicable[b]			

AE = adverse events; FMQ = Food and Drug Administration medical query; MedDRA = medical dictionary for regulatory activities; N = total number of subjects; n = number of subjects in each category; SMQ = standardised MedDRA query; SOC = system organ class

[a] The following search strategies were employed to identify events: For psychiatric disorders, nervous system disorders, cardiac disorders, vascular disorders, and infections and infestations, the corresponding SOC was used. For accidents and injuries, cerebrovascular disorders, and anti-cholinergic syndrome, the Accidents and injuries, Central nervous system vascular disorders, and Anticholinergic syndrome SMQ was used. For Quality of Life decreased, the PTs "Impaired quality of life" and "Quality of life decreased" were searched. For the last category (sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, and fractures), the Fall and Fracture FMQs provided in the appendix were used. The search terms associated with each category are provided in an appendix.

[b] Overall numbers of "other AE" are too low to provide meaningful differences.

Source: EU-Q94 Table 2

The safety profile for subjects aged ≥75 enrolled in CB8025-32048 and CB8025-31731-RE (which does not have an upper age limit) treated with seladelpar appeared overall similar to the general population, although for a limited population.

The lack of extensive safety data in the elderly population is reflected in the SmPC section 4.2 clarifying that limited data exists in elderly patients but that no dose adjustment is required, as no safety concerns due to age were identified.

Additional safety information will be obtained in subjects ages ≥75 in ongoing study CB8025-31731-RE and placebo-controlled confirmatory study CB8025-41837, neither of which has an upper age limit for enrolment.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Several drug interaction studies were conducted, which are discussed and assessed in the Pharmacokinetics section above.

2.6.8.8. Discontinuation due to adverse events

The rate of study drug discontinuation due to TEAEs was low. In the controlled clinical studies for seladelpar, the incidence of TEAEs leading to discontinuation of study drug was similar across treatment groups, seladelpar 3.1% vs placebo 4.6% in pivotal study CB8025-32048 and 2.2% in the seladelpar 10 mg and 5 mg groups vs 2.3% in the placebo group of supportive study CB8025-31735. The only event occurring in more than 1 subject was pruritus in supportive study CB8025-31735, occurring in one patient in the 5 mg group and one in the 10 mg group. No patients discontinued due to pruritus in pivotal study CB8025-32048.

Dose reductions to 5 mg or temporary treatment interruptions were allowed in the clinical programme. The incidence of TEAEs leading to study drug interruption was similar between the seladelpar and placebo arms in both pivotal study CB8025-32048 and supportive study CB8025-31735. Only 1 patient had a dose reduction in pivotal study CB8025-32048. As only the 10 mg capsule is included in this MAA, information in the SmPC on criteria for dose reduction would not be applicable currently.

During the development programme of seladelpar, studies have been terminated early due to two suspicious safety findings. A phase 2 study CB8025-21730 on NASH was terminated early due to atypical histological findings which were later concluded to not be related to seladelpar. A phase 2 study CB8025-21528 with seladelpar 50 and 200 mg was terminated early due to dose-dependent increases in transaminases.

2.6.8.9. Post marketing experience

No post-marketing data were presented.

2.6.9. Discussion on clinical safety

Exposure

The pivotal study CB8025-32048 randomised a total of 193 subjects on a 2:1 basis to seladelpar 10 mg once daily (128 subjects) or placebo (65 subjects). Mean exposure was 50.5 weeks in the seladelpar arm and 48.3 weeks in the placebo arm. The population was predominantly female and white, with mild PBC in the majority of subjects (82.8% in the seladelpar 10 mg group, and 92.3% in the placebo group), no subjects had a Rotterdam score reflecting advanced disease. No patients exposed to seladelpar had decompensated hepatic impairment (Child-Pugh B or C).

Supportive study CB8025-31735 randomised a total of 265 subjects on a 1:1:1 basis to seladelpar 5 mg: 89 subjects, 10 mg: 89 subjects, placebo: 87 subjects. The population was also predominantly female and white, with mild PBC in the majority of subjects. This study was terminated early due to suspicious findings in the phase 2 NASH study (CB8025-21730), resulting in mean duration of

exposure similar between the placebo (17.8 weeks), and seladelpar 5 mg and 10 mg (17.6 weeks each) treatment groups.

The safety database includes 1452 subjects, of which 293 subjects received placebo and 1159 subjects received at least 1 dose of seladelpar. In controlled and uncontrolled studies, 379 PBC patients were exposed to 10 mg seladelpar for ≥ 26 weeks (6.5 months). Of these, 314 PBC patients were exposed to 10 mg seladelpar for ≥ 52 weeks. The safety database is of an acceptable size taking into account the rarity of the disease. Duration of treatment was 1 year in controlled studies.

Interim results from supportive uncontrolled long-term study CB8025-31731-RE as of 31 January 2024 reported a total of 124 subjects with continuous exposure to seladelpar 10 mg for ≥ 2 years, with small numbers of subjects (n=30) having received continuous treatment for 3 years.

The data collection was done in an acceptable way for all studies. Laboratory values, liver biopsies and ultrasound were included. It was focused on signs of hepatic and renal toxicities as well as muscle and pancreatic toxicities, which is meaningful in light of the non-clinical and class characteristics.

Treatment-emergent adverse events (TEAEs)

At the recommended dose of 10 mg once daily, seladelpar was well tolerated over 52 weeks of treatment in subjects with PBC in the pivotal study CB8025-32048. The incidence of TEAEs was similar between the seladelpar 10 mg group, 111 (86.7%), and the placebo group, 55 (84.6%). Common TEAEs by PT that occurred at a ≥ 1% higher incidence in the seladelpar arm relative to the placebo arm were COVID-19 (18.0% vs 15.4%), headache (7.8% vs 3.1%), abdominal pain (7.0% vs 1.5%), nausea (6.3% vs 4.6%), and abdominal distension (6.3% vs 3.1%). Except for COVID-19, these were accepted to be included in section 4.8 of the SmPC based on a numerical imbalance of events in the seladelpar group versus the placebo group in the pivotal study.

In supportive study CB8025-31735 with shorter duration, the overall incidence of TEAEs was lower in the seladelpar 10 mg and 5 mg groups (65.2% and 62.9%, respectively) compared with the placebo group (73.6%).

In pivotal study CB8025-32048, TEAEs assessed as treatment-related by the Investigator were reported in 22 (17.2%) of subjects in the seladelpar 10 mg group and 8 (12.3%) of subjects in the placebo group. 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%).

Further analysis of pooled data from both the pivotal study CB8025-32048 and supportive study CB8025-31735, and similarly, analysis of treatment-related TEAEs as investigator assessed from pooled data, resulted in ADRs Dizziness and Diarrhoea with higher incidence in the seladelpar group. However, there was insufficient evidence to suggest a causal association with either of these potential ADRs.

Frequencies of the adverse drug reactions in section 4.8 of the SmPC were based on pooled data from pivotal study CB8025-32048 and supportive study CB8025-31735. Abdominal pain, along with similar PTs of abdominal pain upper, abdominal discomfort, and abdominal pain lower were pooled together, resulting in a frequency of 'Very common (≥ 1/10)'. For ADRs Headache, Nausea, and Abdominal distension the frequency 'Common (≥ 1/100 to < 1/10)' was calculated.

In pivotal study CB8025-32048, treatment-emergent SAEs were reported in similar incidences in the seladelpar 10 mg group (9 (7.0%)) and the placebo group (4 (6.2%)). Each SAE was reported in only 1 subject (except COVID-19), and none of them were assessed as treatment-related by the Investigator.

There were no deaths in the pivotal study. Two subject deaths were reported in the seladelpar PBC development programme, both in long-term studies. One due to malignant neoplasm of unknown primary site that occurred 7 months after the last dose (CB8025-31731) (CB8025-31731-RE); both fatal events were considered unrelated to seladelpar.

Interim results as of 31 January 2024 were presented from supportive uncontrolled long-term study CB8025-31731-RE, where a total of 124 subjects had continuous exposure to seladelpar 10 mg for ≥ 2 years. Continuous exposure to seladelpar 10 mg does not appear to cause an increase in number of reported TEAEs with increasing length of treatment, but rather a decrease, although with small numbers of subjects having received treatment for 3 years. As the available information is insufficient to determine whether or not the long-term use could constitute a safety concern, but long-term use is expected. Long-term safety has been added to the Summary of Safety Concerns in the RMP as a category of Missing information.

Non-clinical data raised concerns for malignancies developing with seladelpar treatment. Data on malignancies from the full clinical programme was presented and discussed in light of the non-clinical concerns. This revealed a cluster of skin related malignancies in the seladelpar group that was not reflected in the placebo group. However, due to a large difference in follow-up time, these groups were not entirely comparable. In addition, numbers on incidence of skin related malignancies in the population presented from the literature was similar to what was found in the clinical studies. Thus, malignancies in humans are not considered to be a potential risk at this time.

In pivotal study CB8025-32048, the incidence of TEAEs leading to discontinuation of study drug was similar across treatment groups (seladelpar 3.1% vs placebo 4.6%) with no event occurring in more than 1 subject. Dose reductions from 10 mg to 5 mg or treatment interruptions were accepted in the clinical studies. Currently, only a capsule of 10 mg seladelpar is included in the MAA.

Safety of special interest

Hepatotoxicity

Hepatotoxicity in the form of Grade 3 ALT elevations occurred in 3 PBC patients in a phase 2 study CB8025-21528 with higher doses of seladelpar (50 mg and 200 mg), causing an early termination of the study. The transaminase elevations were rapid, asymptomatic and reversible upon treatment discontinuation. Information on the study results is included in section 4.9 of the SmPC.

In the pivotal study CB8025-32048, a lower percentage of subjects in the seladelpar group than in the placebo group experienced at least 1 liver-related TEAE (8 (6.3%) vs. 6 (9.2%)), and greater postbaseline reductions in ALP, ALT, and GGT were observed in the seladelpar group. No DILI cases were noted. Fewer subjects treated with seladelpar than subjects who received placebo met the criteria for liver biochemistry parameters of interest in at least 1 category (11 (8.6%) vs. 10 (15.4%)). On an individual level, Grade 2 shifts from baseline were noted for AST respectively ALT in 2 respectively 3 subjects in the seladelpar group compared to none in the placebo group.

Considering the 3 severe Grade 3 ALT elevations reported in the earlier high-dose study (CB8025-21528), it is reassuring that the 5 AST/ALT elevations noted in the pivotal study were moderate Grade 2. TEAEs potentially reflecting liver-related toxicity were not more frequent in the seladelpar 10 mg group and most of the occurring events were mild to moderate which is also reassuring. Thus, it could be that the risk for severe transaminase elevations is dose dependent and not occurring at the dose level now targeted for authorisation, 10 mg. This will however warrant continuous monitoring henceforth. The proposed monitoring of liver test abnormalities and subsequent treatment adjustments in SmPC section 4.4 is endorsed. The risk for hepatotoxicity is also reflected in the RMP as an important potential risk.

Renal-related toxicity

Dose-dependent elevation of serum creatinine occurred in PBC patients in a phase 2 study CB8025-21528 with higher doses of seladelpar (50 mg and 200 mg). Creatinine elevations were asymptomatic and reversible upon treatment discontinuation.

There were no renal-related TEAEs reported in pivotal study CB8025-32048. However, seladelpar was associated with an increase in the subject incidence of renal safety laboratory parameters of interest (12 (9.4%) subjects in the seladelpar 10 mg arm; 1 (1.5%) subject in the placebo arm). All these 13 subjects met criteria for eGFR decrease ≥ 25% from baseline, and 1 subject in the seladelpar 10 mg arm also met criteria for creatinine increase ≥ 1.5× baseline. Median increases in the creatinine values from baseline of up to 6.6% were observed with the 10 mg dose compared with up to 2.2% in subjects taking placebo. Most of the subjects had resolution at the next study visit without change in study drug. Overall, changes were mild, of variable time to onset and there were no associated TEAEs.

In supportive study CB8025-31735, there was an imbalance in TEAEs in the Renal and Urinary Disorders SOC with more cases in the seladelpar groups, but numbers are small.

While laboratory parameters of interest were not examined in other studies, small increases in creatinine and corresponding reductions in eGFR were observed in subjects treated with seladelpar at all doses.

A mechanism for increased levels of creatinine has not been established, but it has been proposed that rather than a decline in renal function, PPARα and mixed PPARα/δ agonists increase the metabolic production rate of creatinine independent of muscle cell lysis, or a decrease in creatinine clearance without a change in glomerular filtration rate. Post-hoc analyses using an alternative cystatin C-based equation to calculate eGFR further supported that changes were not reflective of a true decline in renal function.

Muscle-related toxicity

Because the non-clinic testing of seladelpar had shown muscle toxicity and because myopathy and rhabdomyolysis have been observed with marketed PPARα and pan-PPAR agonists these were areas of interest. In study CB8025-21528, one subject receiving seladelpar 200 mg developed an AE of myopathy associated with elevated CK. However, in pivotal study CB8025-32048 and likewise in the supportive studies, no safety concerns related to muscle toxicity were seen.

Safety in special populations

There were no pregnant subjects and no subjects with hepatic impairment CP-B or C in the pivotal study CB8025-32048. Only one subject, in the active treatment group, had renal impairment and reported no SAEs or AEs leading to discontinuation. No other relevant special populations were reported.

Subjects with hepatic impairment

The target population of this medicinal product is to a large extent expected to have (or subsequently develop) an impaired hepatic function. Thus, clinical consequences of any hepatic injuries from the active substance would likely be more critical in these patients. Seladelpar seems to be mainly eliminated via metabolism. This in combination with signals regarding hepatic safety with higher doses of seladelpar from previous studies leads to an extra requirement for the characterisation of safety in individuals with impaired hepatic function.

Safety of seladelpar in subjects with cirrhosis and varying degrees of hepatic impairment (HI) was assessed in two phase 1 studies. In general, exposure to seladelpar increased with increasing HI, but no safety concerns were identified during dosing of limited duration (≤ 28 days).

In pivotal study CB8025-32048, no patients with advanced PBC severity according to Rotterdam criteria were included, and in the seladelpar arm only 17.2% of the patients had moderately advanced PBC. In keeping with study entry criteria, nearly all subjects with cirrhosis in phase 2 or phase 3 studies were CP-A. Thus, the safety of seladelpar in PBC subjects with advanced PBC and moderate (CP-B) or severe (CP-C) HI has not been established. Patients with elevated bilirubin at baseline who received 10 mg seladelpar and continued to uncontrolled long-term study CB8025-31731-RE comprised 52 subjects. Exposure-adjusted numbers for subjects with at least one TEAE appeared to increase with each year of treatment, reflecting a population with slightly more severe disease.

PBC is a progressive disease. In SmPC section 4.2 it is reflected, that treatment discontinuation should be considered if the patient progresses to moderate hepatic impairment, and use is not recommended in patients with severe hepatic impairment. In addition, section 4.4 of the SmPC includes information on monitoring of hepatic impairment and measures to take in case of worsening liver tests. Use in PBC patients with moderate (Child Pugh B) hepatic impairment is listed as missing information in the RMP.

Seladelpar as monotherapy

Few patients were included in pivotal study CB8025-32048 receiving seladelpar as monotherapy (8 subjects, 6.3% and 4 subjects, 6.2% in the seladelpar and placebo groups, respectively). In the placebo group, i.e. patients with neither UDCA nor seladelpar treatment, 4 of 4 subjects (100.0%) experienced TEAEs, compared to 5 of 8 subjects (62.5%) in the seladelpar 10 mg monotherapy group. In the overall seladelpar population of this study, 111 (86.7%) subjects experienced ≥ 1 TEAE. Thus, although the monotherapy group had a too limited sample size to draw firm conclusions, the safety profile appears overall similar to that of subjects who received seladelpar in combination with UDCA.

Elderly patients

In the pivotal study CB8025-32048, age at screening was between 28-75 years. Only 41 subjects over 65 years were included of a total of 193; 29 (22.7%) in the seladelpar group and 12 (18.5%) in the placebo group. Total subjects with an AE were comparable between the seladelpar age groups below and above 65 years (86 (86.9%) vs 25 (86.2%)). The safety profile among subjects aged ≥65 appeared overall similar to the younger population, with some numerical imbalances with certain categories occurring more frequently in subjects treated with seladelpar and certain categories of events occurring more frequently in placebo. The lack of extensive safety data in the elderly population is reflected in the SmPC section 4.2 clarifying that limited data exists in elderly patients but that no dose adjustment is required, as no safety concerns due to age were seen.

Pregnancy

In the SmPC section 4.6 it is reflected that as a precautionary measure**,** it is preferable to avoid the use of seladelpar during pregnancy. Overall, only two pregnancies have been documented, both in study CB8025-31731-RE: 1 subject elected to terminate the pregnancy and continue treatment, and the other subject discontinued treatment but remained on study as of the data cutoff date. This subject did not experience any AEs during the pregnancy. The risk for Use in Pregnancy is considered sufficiently reflected in SmPC section 4.6 and is included in the RMP as Missing Information.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Additional safety data needed in the context of a conditional MA

The applicant commits to provide comprehensive clinical data post authorisation based on the ongoing AFFIRM (CB8025-41837) study (see study description in the efficacy part of this assessment). The main purpose of this study is to provide comprehensive data on efficacy based on clinical outcomes but also the following safety concerns as described in the RMP will be addressed with this study over 156

weeks of treatment compared with placebo:

- Hepatotoxicity,
- Use in PBC patients with moderate (Child Pugh B) hepatic impairment and
- Long term safety

2.6.10. Conclusions on the clinical safety

The safety database is considered sufficiently large considering that PBC is an orphan condition. Duration of treatment was only 1 year in controlled studies. Therefore, long-term safety has been included as Missing information in the RMP.

Overall, the safety profile of seladelpar 10 mg once daily appears comparable to that of placebo once daily. Dose-dependent elevations in transaminases (ALT and AST) and serum creatinine were noted with higher than applied for doses of seladelpar (50 mg and 200 mg), but severe elevations were not evident at 10 mg. Hepatotoxicity is included as an important potential risk in the RMP.

The safety of seladelpar in PBC patients with advanced PBC and moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment has not been established. This is a concern as PBC is a progressive disease. Therefore, the prescriber is advised to consider discontinuing seladelpar if the patient progresses to moderate hepatic impairment. Use is not recommended in patients with severe hepatic impairment. Appropriate guidance on measures to take in case of disease progression are included throughout the SmPC and use in PBC patients with moderate (Child Pugh B) hepatic impairment is listed as missing information in the agreed RMP.

The above-described safety concerns will be followed up within the category 3 study CB8025-31731-RE (ASSURE) and CB8025-41837 (AFFIRM) which is a Specific Obligation to this Conditional Marketing Authorisation.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

Description	**Due date**
In order to confirm the efficacy and safety of seladelpar in 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, the MAH shall conduct and submit the final results of the phase III randomised, placebo- controlled clinical study (AFFIRM) to evaluate the efficacy and safety of seladelpar on long-term clinical outcomes in adults with Primary Biliary Cholangitis (PBC) and compensated cirrhosis according to an agreed protocol	August 2030

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None

Summary of safety concerns	
Important potential risks	Hepatotoxicity
Missing information	Use in Pregnancy
	Long term safety
	Use in PBC patients with moderate (Child Pugh B) hepatic impairment

2.7.2. Pharmacovigilance plan

Summary Table of additional Pharmacovigilance activities

Table 48: On-going and planned additional pharmacovigilance activities

Study status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due date**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study CB8025-21838. The Effect of Hepatic Impairment on the Pharmacokinetics of Seladelpar: An Open-Label Study Following Oral Dosing of Seladelpar to Subjects with Primary Biliary Cholangitis (PBC) and Hepatic Impairment Ongoing	Primary Objectives: • Evaluate the pharmacokinetic (PK) profiles of seladelpar and major metabolites: M1, M2 and M3 after a single and multiple oral doses in PBC subjects with HI • Evaluate the safety and tolerability of seladelpar after a single dose and multiple oral doses in PBC subjects with HI Secondary Objectives: • Evaluate the urinary PK of seladelpar and its major metabolites: M1, M2 and M3 in PBC subjects with HI • Evaluate the relationship between plasma seladelpar PK parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) and albumin, bilirubin, PT, and Child-Pugh score	Hepatotoxicity Use in PBC patients with moderate (Child Pugh B) hepatic impairment	Interim report Study completion Final Study Report	dated 16 Nov 2023 (data cut off 13 Oct 2023) January 2025 June 2025

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due date
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 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 Study Completion Final Study Report	13 Nov 2023 (data cut off 29 Jun 2023) November 2028 August 2029

2.7.3. Risk minimisation measures

Summary of risk minimisation measures

Table 49: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks: None		
Important Potential Risks		
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 CB8025-21838 Study CB8025-31731-RE
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 CB8025-21838 Study CB8025-31731-RE

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14.08.2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Seladelpar Gilead (Seladelpar lysine dihydrate) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

PBC is a serious and potentially life-threatening autoimmune disease of the liver characterised by inflammation and destruction of intrahepatic bile ducts resulting in cholestasis and accumulation of toxic bile acids. It can progress to liver fibrosis, cirrhosis, and hepatic failure, and is one of the top 6 indications for liver transplantation in the EU and US, despite being a rare disease. Clinical symptoms include pruritus, which can be severe, and affects up to 70% of patients. The main goal of treatment is to prevent disease progression to decompensated cirrhosis, liver transplantation or death.

The indication initially proposed by the applicant was:

Livdelzi is indicated for the treatment of primary biliary cholangitis (PBC) including pruritus in adults without cirrhosis or with compensated cirrhosis (Child-Pugh A) 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 indication was not considered acceptable by the CHMP since the mechanism of action is supposed to be part of 5.1 of the SmPC and references to study endpoints (i.e. *including pruritus)* should, in general, not be included in 4.1. Furthermore, the applicant approved the name "Seladelpar Gilead" for this medicinal product for implementation. Hence, the applicant amended their indication claim as follows:

Seladelpar Gilead 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.

3.1.2. Available therapies and unmet medical need

The first-line therapy for PBC is UDCA, a noncytotoxic bile acid that has been the mainstay of treatment for more than 20 years. However, despite receiving UDCA, up to 40% of patients have persistent elevation of ALP and/or bilirubin and are considered inadequate responders. Intolerance to UDCA may also occur and is seen in up to 5% of patients. Obeticholic acid (Ocaliva, OCA) was conditionally approved by the EMA and FDA in 2016 based on the surrogate endpoints of ALP levels and total bilirubin levels in patients with PBC who were inadequate responders to or intolerant to UDCA. Due to the failure to show effect on clinically important event, the marketing authorisation of OCA was revoked following assessment within referral. A new treatment, Iqirvo (elafibranor) was recently approved under conditional marketing authorisation (September 2024) for PBC not responding to /intolerant to UDCA by showing a beneficial effect on biomarkers, but no significant effect on pruritus.

UDCA and Iqirvo have no clinical benefits for cholestatic 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 significant side effects. There remains an unmet need for a therapy that both slows progression of disease and improves clinical symptoms.

3.1.3. Main clinical studies

Pivotal Phase 3 study RESPONSE (CB8025-32048)

This was a phase 3, double-blind, randomised, placebo-controlled, multicentre study conducted in subjects with a diagnosis of PBC and an inadequate response or intolerance to UDCA. The study evaluated oral seladelpar 10 mg once daily versus placebo over 52 weeks. The study drug was given on top of UDCA in the majority of the subjects or as monotherapy if the patients were intolerant to UDCA. Eligible subjects in the RESPONSE study were 18-75 years old with PBC and should have an elevated ALP (ALP≥1.67xULN) despite an at least 1-year therapy with UDCA (or intolerance of UDCA)

The study included 193 subjects randomised to seladelpar (n=128) and placebo (n=65).

3.2. Favourable effects

The primary endpoint in the pivotal study was the response to treatment based on 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). Various supplementary analysis confirmed the primary analysis.

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).

The second multiplicity controlled key secondary endpoint, change from baseline to month 6 in weekly averaged pruritus NRS in patients with a baseline pruritus score of ≥4, was also 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).

Other endpoints examining the biomarkers (non-multiplicity controlled) using different cut-off values or timepoints of evaluation were in line with the primary results. A reduction of ALP was apparent at month 1 for most of the patients and sustained through month 12.

Consistent with the results from the analysis of the key secondary efficacy endpoint of changes in Pruritus NRS at Month 6, results from exploratory endpoints such as LS mean changes in the Itch Domain of the PBC-40 QoL from baseline to Month 6 were -2.20 in the seladelpar arm vs -0.40 in the placebo arm and the LS mean change from baseline to month 6 in the total score of the 5-D Itch scale was -4.7 in the seladelpar arm compared with -1.3 in the placebo arm.

3.3. Uncertainties and limitations about favourable effects

The prognostic value of a biochemical response at Week 52, defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15% is not fully demonstrated. 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 regarding 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.

Since almost all PBC patients had a normal bilirubin value at baseline, the biochemical response was mainly driven by the ALP decrease. A small decrease was however seen also in the bilirubin levels.

There were no significant differences in change of liver stiffness (measured by transient elastography), ELF score or histology findings between the groups.

The information is also limited regarding clinically relevant endpoints, such as progress to decompensated fibrosis, liver transplantation or death. One patient with cirrhosis at baseline in the seladelpar group experienced a PBC clinical outcome events, which was hospitalisation due to variceal bleeding and worsening of liver cirrhosis due to decompensated PBC. The ongoing AFFIRM study is designed to evaluate time to clinically important events and it is expected that the study will be able to provide comprehensive data post authorisation regarding this.

Regarding pruritus, there is limited information regarding the validity of the worst itch NRS in the PBC population. The score has been used in other diseases, mainly dermatological diseases but also in pruritus associated kidney disease. Despite the lack of an adequate validation in the PBC population, the score is considered useful to evaluate itch also in PBC, and a decrease of ≥3 points could be

considered a meaningful important difference. A responder analysis carried out by the applicant, non-multiplicity controlled, showed that 44.9% of the Seladelpar Gilead-treated patients and 21.7% of the controls achieved a ≥3 points reduction of pruritus. It is acknowledged that the study was not powered for a responder analyses.

In the overall population (ITT analysis set, exploratory endpoint), the mean baseline pruritus NRS value was 3.0 in both groups and at month 6, LS mean changes from baseline in weekly averaged Pruritus NRS in the seladelpar arm were -1.3, relative to -0.4 in placebo. Of the patients with NRS >0 at baseline (seladelpar=98, placebo=50), only a few patients achieved an NRS=0 at month 6, with a similar proportion in the seladelpar and placebo groups (16% vs 12%). Thus, not all patients appear to respond similarly to the pruritus reducing effect.

Regarding subgroups, for patients with a more severe disease (such as ALP ≥350 U/L, cirrhotic disease, TB >1) efficacy is lower, with a point estimate around 35% for patients achieving a biochemical response at week 52 in the cirrhotic population. Only a small proportion of patients with cirrhotic disease was included in the pivotal study (14% in respective group) and all had mild hepatic impairment (Child-Pugh A). Information regarding efficacy in patients with moderate or severe hepatic impairment are currently lacking. Additional information regarding efficacy in the cirrhotic population with mild to moderate hepatic impairment may be achieved from the ongoing AFFIRM study, that will include only cirrhotic patients (CP-A and CP-B). Information regarding the lack of data in patients with moderate to severe hepatic impairment and how to manage patients who progresses is adequately described in the SmPC.

Regarding long term efficacy, data are scarce, and no conclusion can be drawn regarding efficacy beyond one year. The ongoing study CB8025-31731-RE will collect open label long term efficacy and safety data up until 5 years. In addition, the AFFIRM study which is Specific Obligation to this Conditional Marketing Authorisation will collect data up until 3 years for each patient. The evidence generated on placebo controlled clinical outcome measures is expected to confirm the efficacy of Seladelpar Gilead in the treatment of PBC which is currently mainly based biochemical response.

3.4. Unfavourable effects

In the pivotal placebo-controlled study, 193 PBC patients were randomised on a 2:1 basis and treated with seladelpar 10 mg once daily (128 subjects) or matching placebo (65 subjects) for 1 year. In total, 379 PBC patients were exposed to 10 mg seladelpar for ≥ 26 weeks (6.5 months). Of these, 314 PBC patients were exposed for ≥ 52 weeks. 124 subjects have had continuous exposure to seladelpar 10 mg for ≥ 2 years in an uncontrolled study, 24 of which had received treatment for 3 years.

Adverse drug reactions

In the pivotal study CB8025-32048, the overall incidence of TEAEs was similar between the seladelpar 10 mg group (86.7%) and the placebo group (84.6%). Approximately 90% of the TEAEs were mild to moderate. Uncontrolled data on continuous exposure to seladelpar 10 mg does not show an increase in reported number of TEAEs with increasing length of treatment.

In the pivotal study, common TEAEs by PT that occurred at a ≥ 1% higher incidence in the seladelpar arm relative to the placebo arm were headache (7.8% vs 3.1%), abdominal pain (7.0% vs 1.5%), nausea (6.3% vs 4.6%), and abdominal distension (6.3% vs 3.1%). Frequencies of the adverse drug reactions in section 4.8 were based on pooled data from pivotal study CB8025-32048 and supportive study CB8025-31735. Abdominal pain, along with similar PTs of abdominal pain upper, abdominal discomfort, and abdominal pain lower were pooled together, resulting in a frequency of 'Very common

(≥ 1/10)'. For ADRs Headache, Nausea, and Abdominal distension the frequency 'Common (≥ 1/100 to < 1/10)' was calculated.

Use in elderly

Age at screening was between 28-75 years, only 41 subjects over 65 years were included of a total of 193; 29 (22.7%) in the seladelpar group and 12 (18.5%) in the placebo group. Total subjects with an AE were comparable between the seladelpar age groups below and above 65 years (86 (86.9%) vs 25 (86.2%)).

Hepatic safety

Hepatotoxicity in the form of Grade 3 ALT elevations occurred in 3 PBC patients in a phase 2 study CB8025-21528 with higher doses of seladelpar (50 mg and 200 mg), causing an early termination of the study. The transaminases elevations were rapid, asymptomatic and reversible upon treatment discontinuation.

In the pivotal study CB8025-32048, a lower percentage of subjects in the seladelpar group (8 (6.3%)) than in the placebo group (6 (9.2%)) experienced at least 1 liver-related TEAEs. Fewer subjects treated with seladelpar than subjects who received placebo met the criteria for in at least one liver biochemistry parameters (11 (8.6%) vs. 10 (15.4%)). On an individual level, a shift of 2 CTCAE grades from baseline to worst postbaseline results were noted for AST respectively ALT in 2 respectively 3 subjects in the seladelpar group compared to none in the placebo group. No DILI cases were noted in this study.

Subjects with hepatic impairment

In pivotal study CB8025-32048, a total of 25 (13.0%) subjects (20 (15.6%) and 5 (7.7%) subjects in the seladelpar 10 mg and placebo arms, respectively) had elevated total bilirubin (> 1.0× ULN) at baseline. A higher percentage of subjects with elevated total bilirubin had a TEAE, treatment-emergent SAE, or ≥ Grade 3 TEAE, compared with subjects with normal baseline total bilirubin in both the seladelpar 10 mg and placebo arms. The elevated bilirubin subpopulation who received 10 mg seladelpar in uncontrolled long-term study CB8025-31731-RE comprised 52 subjects. Exposure-adjusted numbers for subjects with at least one TEAE tended to increase with each year of treatment, but with few patients.

Renal safety

Dose-dependent elevation of serum creatinine occurred in PBC patients in a phase 2 study CB8025-21528 with higher doses of seladelpar (50 mg and 200 mg). Creatinine elevations were asymptomatic and reversible upon treatment discontinuation.

In pivotal study there were no renal-related TEAEs reported. The incidence of renal safety laboratory parameters of interest was higher in the seladelpar arm (12 (9.4%)) compared to the placebo arm (1 (1.5%)), all meeting the criteria for eGFR decrease ≥ 25% from baseline, and 1 subject in the seladelpar 10 mg arm also met criteria for creatinine increase ≥ 1.5× baseline. Most of the subjects had resolution at the next study visit without change in study drug.

Malignancy

A cluster of skin related malignancies was noted in the pooled seladelpar group that was not reflected in the placebo group. For the placebo group, subjects sum of exposure in years was 89.9 years. For patients treated with seladelpar 10 mg subjects sum of exposure was 865.1 years. Numbers on incidence of skin related malignancies in the population presented from the literature was similar to what was found in the clinical studies.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety

Duration of treatment was 1 year in the controlled pivotal study, where 128 patients received seladelpar 10 mg once daily and 65 patients received placebo. In an uncontrolled study, a total of 124 subjects have had continuous exposure to seladelpar 10 mg for ≥ 2 years, with small numbers of subjects (n=30) having received continuous treatment for 3 years. The available information is insufficient to determine whether or not long-term use could constitute a safety concern. Long-term safety is included in the RMP as Missing Information.

Use in elderly patients (> 75 years)

Limited data exists in elderly patients. There are no safety data available in subjects 75 years and above and the safety profile in this population is unknown. However, the safety profile among subjects aged ≥65 appeared overall similar to the younger population. The lack of extensive data in the elderly population is reflected in the SmPC.

Hepatotoxicity

Considering the 3 severe Grade 3 ALT elevations reported in the earlier high-dose study (CB8025-21528), it is reassuring that the 5 AST/ALT elevations noted in the pivotal study were moderate Grade 2, and that TEAEs potentially reflecting liver-related toxicity were not more frequent in the seladelpar 10 mg group and that most of the occurring events were mild to moderate. Thus, it may be considered that the risk for severe transaminase elevations seems dose dependent and may not occur at the dose level now targeted for authorisation, 10 mg. It will however be something to continue monitoring henceforth. The proposed monitoring of liver tests in SmPC section 4.4 is endorsed. The risk for hepatotoxicity is also reflected in the RMP as an important potential risk.

Subjects with hepatic impairment

In keeping with study entry criteria, nearly all subjects with cirrhosis in phase 2 or phase 3 studies were CP-A, and most had mild PBC. Thus, the safety of seladelpar in PBC subjects with advanced PBC and moderate (CP-B) or severe (CP-C) hepatic impairment has not been established. This is reflected in SmPC section 4.2, that treatment discontinuation should be considered if the patient progresses to moderate hepatic impairment, and use is not recommended in patients with severe hepatic impairment. In addition, section 4.4 of the SmPC includes information on monitoring of hepatic impairment and measures to take in case of worsening liver tests. The lack of data in patients with moderate hepatic impairment is also reflected in the RMP as Missing Information.

Renal safety

There are some uncertainties with regard to renal safety as dose-dependent increases in serum creatinine were noticed in high dose (50 mg and 200 mg) phase 2 study CB8025-21528. Reassuringly, creatinine elevations were asymptomatic and reversible upon treatment discontinuation in this study. A mechanism for increased levels of creatinine has not been established, but it has been proposed that PPARα and mixed PPARα/δ agonists increase creatinine with no bearing on declining renal function.

Malignancy

The tumours in liver, testis, pancreas and non-glandular stomach observed in the non-clinical carcinogenicity studies are not considered to be of human relevance. The increased incidence of benign epithelial neoplasms in the ovary observed at the low and intermediate seladelpar doses, but not at the high dose, in the 2-year mouse study are considered of uncertain relation to seladelpar-treatment. Overall, these neoplasms are not likely to constitute a human risk.

Clinical data revealed a cluster of skin related malignancies in the pooled seladelpar group that was not reflected in the placebo group. However, due to a large difference in follow-up time, these groups were not entirely comparable. In addition, numbers on incidence of skin related malignancies in the population presented from the literature was similar to what was found in the clinical studies. Thus, malignancies in humans are not considered to be a potential risk at this time.

Pregnancy

In the SmPC section 4.6 it is reflected that as a precautionary measure, it is preferable to avoid the use of seladelpar during pregnancy. Overall, only two pregnancies have been documented, neither had exposure to seladelpar. Use in Pregnancy is included in the RMP as Missing Information.

3.6. Effects Table

Table 50: Effects Table for LIVDELIZI

Effect	Short Description	Unit	Seladelpar 10 mg	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Biochemical responders at Week 52	ALP <1.67 x ULN, TB ≤ULN, and ALP-decrease ≥15%	% (95% CI)	61.7% (53.3, 70.1)	20.0 (10.3, 29.7)	The prognostic value of this endpoint is currently under discussion P<0.0001	CB8025-32048
Responders with normal ALP at Week 52	ALP <1xULN	% (95% CI)	25% (17.5, 32.5)	0 (0.0; 0.0)	The prognostic value of this endpoint is currently under discussion p<0.0001	CB8025-32048
Change from baseline to month 6 in worst itch score NRS in patients with score≥4 at baseline.	Numerical rating scale 0 (no itch) to 10 (worst imaginable itching)	LS mean (SE)	-3.2 (0.28)	-1.7 (0.41)	The clinical relevance of the findings is questioned. Difference -1.5 (-2.5, -0.5) p=0.0047 Support from other exploratory endpoints	CB8025-32048
Unfavourable Effects						
AST/ALT elevation	PBC patients with a 2-grade shift from baseline	n (%)	5 (3.9)	0		CB8025-32048
eGFR decrease	PBC patients with ≥ 25% decrease	n (%)	12 (9.4)	1 (1.5)		CB8025-32048

Effect	Short Description	Unit	Seladelpar 10 mg	Placebo	Uncertainties/ Strength of evidence	References
Abdominal pain	TEAE by PT in PBC patients	n (%)	9 (7.0)	1 (1.5)		CB8025-32048

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Pruritus is recognised as one of the important and common symptoms during the course of the diseases and currently, no PBC treatment is approved in the EU that alleviates cholestatic pruritus. Thus, a treatment affecting also pruritus symptoms is of great importance.

Treatment with Seladelpar Gilead demonstrated a highly 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). Various supplementary analysis confirmed the primary analysis.

However, the main goal in treatment of PBC is to prevent the progression to end stage liver disease and neither a biochemical response nor a reduction of pruritus can act as a certain predictive surrogate marker for this. Long term-data are scarce with only uncontrolled data for treatment beyond one year. Additional information on clinically relevant outcome events will need to be provided from the ongoing study AFFIRM which is a specific obligation to this Conditional Marketing Authorisation.

With respect to safety, hepatotoxicity in the form of Grade 3 ALT elevations was previously documented in a phase 2 study with higher doses of seladelpar (50 mg and 200 mg). Unfavourable effects seen in studies with the proposed dose were mostly non-serious (of low clinical impact), with no signals of liver related issues. Descriptions of the unfavourable effects observed and monitoring recommendations in the SmPC are deemed acceptable management. Furthermore, hepatotoxicity is followed up as an important potential risk within the risk management plan.

Safety of seladelpar in PBC subjects with advanced PBC and moderate (CP-B) or severe (CP-C) hepatic impairment has not been established. Information in the SmPC on monitoring of liver tests and interruption of treatment in case of worsening status are deemed acceptable management. As per SmPC 4.2. the use in patients with severe hepatic impairment is no recommended.

These safety concerns which also concern long-term safety are being followed up by means of a category 3 studies CB8025-31731-RE (ASSURE) and CB8025-41837 (AFFIRM) which is a Specific Obligation to this Conditional Marketing Authorisation.

3.7.2. Balance of benefits and risks

Seladelpar is effective in improving biomarkers after 52 weeks of treatment, with effect on reduction of ALP apparent already after 4 weeks and normalisation of ALP in ¼ of the patients. In addition, statistically significant improvement was seen in pruritus score in patients with a moderate to severe pruritus score at baseline. However, the effect on the bilirubin levels is limited and the clinical relevance of the effect seen on the overall biochemical response in relation to liver survival is unknown. Therefore, the beneficial effect in the treatment of PBC is mainly based on a biochemical surrogate endpoint that has a reasonably likelihood to translate into benefits in terms of clinical

outcomes. However, due to the lack of data on clinically relevant outcomes the submitted data package is not considered comprehensive. Accordingly, the applicant committed to provide comprehensive data based on clinical outcomes post-approval by means of study CB8025-41837 (AFFIRM) which is a Specific Obligation to this Conditional Marketing Authorisation. This study, when completed, is considered suitable to confirm the clinical relevance of the treatment effect with Seladelpar Gilead.

Unfavourable effects seen in studies with the proposed dose were mostly non-serious, with no signals of major safety issues. Safety concerns are based on the limited data available. The Important potential risk of Hepatotoxicity and Missing information on Long-term safety and Use in PBC patients with moderate (Child Pugh B) hepatic impairment will be addressed by data to be provided post-authorisation from the category 3 study CB8025-31731-RE (ASSURE) and study CB8025-41837 (AFFIRM) which is Specific Obligation to this Conditional Marketing Authorisation.

3.7.3. Additional considerations on the benefit-risk balance

Comprehensiveness of data

The applicant had initially applied for a full marketing authorisation claiming that the submitted data can be considered as comprehensive. This was not agreed by the CHMP considering that the clinical relevance of the effect seen on biochemical response in relation to liver related endpoints is unknown. No new substantial data has been provided supporting that a beneficial effect on biomarker can serve as surrogates for clinical events. Therefore, the submitted data is not considered as comprehensive.

The applicant has thus provided a justification that all requirements for a conditional marketing authorisation can be considered as fulfilled.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and life-threatening disease. In addition, the product is designated as an orphan medicinal product.

It is agreed with the applicant that PBC is an orphan disease, potentially severe and lethal, with a high unmet need for effective treatments especially to patients not responding to or intolerant to UDCA. Please refer also to chapter 3.1.1. of the benefit risk balance discussion above.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data. The applicant commits to provide comprehensive clinical data based on the currently ongoing AFFIRM (CB8025-41837) study. This is a placebo-controlled, event driven study, with a maximum of 3-year duration for each participant that will be carried out in patients with compensated cirrhosis and PBC. The primary objective of the study will be to evaluate the effect of seladelpar compared to placebo on event-free survival (EFS) were EFS is defined as the time from start of treatment to the first occurrence of any of the following adjudicated events up to Week 156: Death by any cause, Liver transplantation, (MELD) score ≥15, Ascites requiring treatment or Hospitalisation for any of the

following qualifying events: (Oesophageal or gastric variceal bleeding, Hepatic encephalopathy, Spontaneous bacterial peritonitis, Progression to Child-Pugh (CP)-C). Based on the provision of placebo-controlled data on clinical outcomes it is expected that this study will be able to confirm the efficacy of Seladelpar Gilead in the treatment of PBC and address the current safety concerns on Hepatotoxicity, long-term safety and Use in PBC patients with moderate (Child Pugh B) hepatic impairment. The applicant implemented measures in the protocol to ensure adequate enrolment and data generation such as a more conservative hazard rate estimate and annual drop-out rate and a required elevated baseline ALP to ensure higher risk of clinical events. The applicant has also provided a comprehensive strategy to address potential recruitment delays. This is considered acceptable by the CHMP. The protocol will be submitted by the applicant post-authorisation for final agreement on details on the SAP such as the estimand and tipping point analysis.

- Unmet medical needs will be addressed. The only currently approved treatment for PBC patients not responding/intolerant to UDCA is Iqirvo (elafibranor). Iqirvo recently (sept 2024) received a conditional marketing authorisation for PBC not responding to /intolerant to UDCA by showing a beneficial effect on biomarkers; however, no significant effect was seen on pruritus. Iqirvo is contraindicated in known or suspected pregnancy and in women of childbearing age who do not use contraception. Considering that seladelpar, in addition to having an effect on biomarkers, shows a beneficial efficacy on reducing pruritus, a major problem for several patients with PBC, it is expected that seladelpar will address an unmet medical need present in PBC.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. As discussed above, the immediate availability of Seladelpar Gilead (seladelpar) allows for the treatment of patients who cannot be treated with current treatment options such as patients unresponsive to UDCA which is first line treatment of PBC. Furthermore, Seladelpar Gilead shows a beneficial effect on pruritus which is a main symptom of PBC. In combination with the innocuous safety profile, immediate availability to patients is considered to outweigh the risks although additional data regarding clinically relevant outcomes are still required to render the dataset comprehensive.

Input from the European Association for the Study of the Liver (EASL)

The EASL pointed out that PBC is a rare disease but a leading cause of liver transplantation, illustrating (although slowly evolving) a life-threatening disease with limited treatment options. Disease course is very variable. Since up to 40% are not adequately responding or intolerant to UDCA efficacious treatment represents an unmet need. The EASL also consider the definition of response used "alkaline phosphatase level < 1.67 ULN with > 15% decline from baseline and normal bilirubin" to be a validated surrogate for clinical outcome since it has (based on UDCA treatment) been associated with improved outcomes at 10 years. They further state that biochemical response is an important indicator of efficacy in PBC. A discussion regarding mode of action of new, not yet approved second line treatments, or off label treatment (i.e., bezafibrate) was provided with focus on peroxisome-proliferator activated receptors and the difference in expected anti-cholestatic effect depending on which isotype of receptors to activate (e.g., alpha, delta or combination of several) and also some safety concerns (e.g., concern of PPAR delta in cancer cell survival, however not yet confirmed in the clinical data reported so far). The EASL also highlighted the impaired quality of life in PBC patient, mainly because of pruritus, fatigue and autonomous dysfunction which are not very well correlating with histological and biochemical disease severity markers. In addition, the EASL states that given the reported increased numbers of responders after 2 years compared to 1 year with some compounds, a treatment period of 2 years could be recommended before deciding on non-response.

Input from Albi, which is a patient association approved by the French Ministry of Health

To improve the knowledge of patients 'issues related to PBC treatments, an online survey of PBC patients was conducted to ask them about their treatment. The survey took place in 2020. The survey received 614 usable responses. 93% of participants were treated with UDCA, 16% patients were treated with fibrates, 8% were treated with Ocaliva. The majority of the respondents consider the effect to be very beneficial or rather beneficial. Some side effects were mentioned, sometimes leading to discontinuing the drug; digestion/transit problems (UDCA), fatigue, pain, nausea (fibrates), deterioration in sleep, joint pain, and pruritus (Ocaliva).

Regarding quality of life, fatigue remains the number 1 problem. For 2 out of 3 patients, it is present, even if only slightly. For 1 in 6 patients, it is "intolerable" or "disabling". Pruritus occasionally remains an unresolved problem. Joint pain and transit disorder (mostly diarrhoea, associated with UDCA) also affects more than 1 in 2 patients. Other problems are insomnia, bloating, dry eyes, digestive problems, dry mouth and loss of libido.

The study also shows that some patients cannot tolerate neither Ocaliva nor fibrates, but patients taking these two treatments are keen to continue them, as they see these treatments as their last chance to avoid liver transplantation, but also as the hope of an improvement in their health.

The ideal treatment should; have no side effects, not be habit-forming, not contain toxic or carcinogenic products, etc., with effective quality control, have security of supply (stock-outs), enable liver function to be restored (regression of fibrosis), particularly in the case of late diagnosis.

3.8. Conclusions

The overall benefit/risk balance of Seladelpar Gilead is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Seladelpar Gilead is not similar to Iqirvo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Seladelpar Gilead is favourable in the following indication(s):

Seladelpar Gilead 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.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product on medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of seladelpar in 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, the MAH shall conduct and submit the final results of the phase III randomised, placebo- controlled clinical study (AFFIRM) to evaluate the efficacy and safety of seladelpar on long-term clinical outcomes in adults with Primary Biliary Cholangitis (PBC) and compensated cirrhosis according to an agreed protocol	August 2030

New active substance status

Based on the CHMP review of the available data, the CHMP considers that Seladelpar is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.