13 December 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Seladelpar Gilead (seladelpar)
Treatment of primary biliary cholangitis
EU/3/17/1930

Sponsor: Gilead Sciences Ireland UC

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Seladelpar
Other name(s)	-
International Non-Proprietary Name	Seladelpar
Tradename	Seladelpar Gilead
Orphan condition	Treatment of primary biliary cholangitis
Sponsor's details:	Gilead Sciences Ireland Unlimited Company IDA Business And Technology Park Carrigtohill Co. Cork T45 DP77 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Larode Ltd
COMP opinion	7 September 2017
EC decision	16 October 2017
EC registration number	EU/3/17/1930
Post-designation procedural history	
Transfer of sponsorship	From Larode Ltd to Cymabay Ireland Limited – EC decision of 30 January 2019 From Cymabay Ireland Limited to Gilead Sciences Ireland Unlimited Company – EC decision of 11 October 2024
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Kristina Dunder / Thalia Marie Estrup Blicher
Applicant	Gilead Sciences Ireland Unlimited Company
Application submission	10 February 2024
Procedure start	29 February 2024
Procedure number	EMA/H/C/004692
Invented name	Seladelpar Gilead
Proposed therapeutic indication	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. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/seladelpar-gilead
CHMP opinion	12 December 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Zsofia Gyulai / Irena Rogovska
Sponsor's report submission	4 March 2024

COMP discussion and adoption of list of questions	5-7 November 2024
Oral explanation cancelled by the COMP	3 December 2024
COMP opinion (adoption via written procedure)	13 December 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2017 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing seladelpar was considered justified based on clinical data demonstrating improvement in markers of cholestasis;
- the condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia;
- the condition was estimated to be affecting approximately 3.9 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing seladelpar will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who have not adequately responded to first line treatment responded well to treatment with seladelpar and achieved normalisation of biomarkers of cholestasis (such as alkaline phosphatase). In addition, these responses compared favourably to those reported with the use of the authorised second line treatment. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing seladelpar as an orphan medicinal product for the orphan indication: treatment of primary biliary cholangitis".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Primary Biliary Cholangitis (PBC) is an auto-immune condition manifesting with chronic, progressive liver disease. PBC is characterised by cholestasis caused by autoimmune destruction of biliary ductules with progressive impairment of bile flow in the liver. This results in increased hepatocellular bile acid

concentrations toxic to the liver. Such hepatocellular injury is associated with a local inflammatory response resulting early on in an abnormal elevation of serum alkaline phosphatase (ALP) levels, a hallmark of the disease.

The clinical features and natural history of PBC vary greatly between patients, ranging from asymptomatic and slowly progressive to symptomatic and rapidly evolving. It affects primarily (90%) women of middle-age. Many asymptomatic patients will, however, develop symptomatic liver disease within 5 years of diagnosis, although a third could remain symptom-free for many years. In untreated patients or in inadequate responders to existing therapies, the disease may progress to hepatic fibrosis, cirrhosis, hepatic decompensation, and death unless they receive a liver transplant. [Kuiper 2010, Kumagi 2008]. PBC has also been identified as an important risk factor for hepatocellular carcinoma [Ali 2015]. In early stage, patients present with ALP (alkaline phosphatase) elevation, and in advanced stage cirrhosis and conjugated hyperbilirubinemia. Symptoms commonly include fatigue, abdominal pain, pruritus, hepatic encephalopathy ("brain fog") and jaundice.

The aetiology of PBC remains largely unknown, although there is an association with anti-mitochondrial antibodies, and disease-specific anti-nuclear antibodies targeting sp100 and gp210 (Rigopoulou EI and Bogdanos DP, World J Gastroenterol. 2023 Mar 28;29(12):1795-1810).

The approved therapeutic indication "SELADELPAR GILEAD is indicated for the treatment of primary biliary cholangitis (PBC), in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA." falls within the scope of the designated orphan condition "treatment of primary biliary cholangitis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

PBC is a progressive inflammatory autoimmune cholestatic liver disease. Without treatment, it leads to further liver injury with potential progression to fibrosis, cirrhosis, and its complications, including end-stage liver disease and potentially death. If left untreated, the median duration of survival for symptomatic patients ranges from 5 to 8 years from the onset of symptoms [Al-Harthy 2012]. The use of UDCA in the 1990s changed the natural history of PBC, and has resulted in decreased histological progression of disease, and lower rates of liver transplantation and death. UDCA is also associated with

a lower risk of hepatic decompensation. Patients from the Globe PBC Study Group diagnosed after the year 2000 had a 10-year incidence rate of cirrhotic decompensation (defined as ascites, esophageal varices bleeding, or hepatic encephalopathy) of 5.8% versus 13.7% in the 1980s. The degree of the biochemical response to UDCA is strongly associated with clinical outcomes [Trivedi 2016].

The most common and burdensome symptoms described in patients with PBC include fatigue and pruritus, which can have a significant negative impact on a patient's quality of life.

In recent decades, patients are being diagnosed earlier and thus are presenting with milder disease severity [Murillo Perez 2018]. Up to 60% of the newly diagnosed cases are asymptomatic with the majority of those diagnosed becoming symptomatic within 10 years [Kumagi 2008].

In conclusion, the condition is considered to be chronically debilitating due to progressive hepatic dysfunction, pruritus, fatigue and abdominal pain and life-threatening due to hepatic failure, cirrhosis and esophageal varices bleeding, and the increased risk of developing hepatocellular cancer.

Number of people affected or at risk

The sponsor has used three publications for the prevalence estimate, two of these were recently published metanalysis.

The two systematic reviews and meta-analyses reporting the prevalence of PBC in Europe were:

1. Gazda et al. estimated a European prevalence of PBC as 22.3 per 100,000 population (95% CI: 18.0, 27.0) from publications between 2000 and 2020. The 17 studies reported rates from 12 countries across Europe (Finland, Spain, Denmark, Iceland, Greece, Netherlands, Ireland, Italy, Croatia, Sweden, Slovakia, and Germany). Local prevalence rates ranged from 10.0 to 58.2 per 100,000 population (Gazda et al., 2021).

2. Lv et al. included all publications on PBC prevalence to October 2020 including 23 prevalence studies from 12 European countries published between 1980 to 2020. The overall European prevalence was reported as 14.6 per 100,000 population (13.6 in 1991 to 2000; 20.7 in 2001 to 2010 and 17.3 in 2011 to 2020). Studies were from across Europe (Estonia, Croatia, Italy, Denmark, Norway, Netherlands, Finland, England, Spain, Iceland, Greece, Ireland, Slovakia, Sweden) and the reported prevalence across studies ranged from 2.7 to 40.8 per 100,000 population (Lv et al., 2021).

Estimates of prevalence from the two meta-analyses since 2000 therefore provided rates of 22.3, 20.7 and 17.3 per 100,000 population. Rates from 2000 or earlier in Lv et al were not included in the estimate for two reasons. Firstly, prevalence is reported to be higher after 2000 and, secondly, data from before 2000 were excluded from the Gazda analysis. The exclusion of the less recent rates meant that there was no data from Estonia and Finland, but regions across the EU were represented. The mean of the 3 post-2000 prevalence rates provided an estimated prevalence of 20.1 (calculated from (20.7 + 17.3 + 22.2)/3) per 100,000 population or 2.0 per 10,000 population.

One additional EU prevalence rate identified was published after the systematic searches were completed. A Swedish study reported a 2019 prevalence of 1.9 per 10,000 population (Nasr et al., 2023) which is consistent with the trans-European meta-analysis results.

The sponsor concluded that the prevalence hasn't changed much since 2000 and that there was no need to consider changes in trends. They proposed a final estimate of in 2 in 10,000 which the COMP accepted.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are only two authorised medicinal products in the EU for the treatment of PBC: ursodeoxycholic acid (UDCA), and Iqirvo. Ocaliva (obeticholic acid, OCA) has recently had its conditional licence withdrawn by the European Commission and is no longer authorised for use in the primary biliary cholangitis.

Seladelpar Gilead has the following indication: *SELADELPAR GILEAD is indicated for the treatment of primary biliary cholangitis (PBC), in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA*

Ursodeoxycholic acid (UDCA)

UDCA is a hydrophilic, noncytotoxic bile acid and represents the universal first-line standard of care treatment for PBC [Corpechot 2005]. UDCA is currently approved nationally or decentralised in EU member states for the treatment of of primary biliary cirrhosis. In international treatment guidelines, its use is recommended as a first-choice treatment option, based on long-term experience and evidence of slowing disease progression, and improved transplant-free survival [Corpechot 2011]. Nevertheless, up to 40 percent of patients have persistent elevation of AP and/or bilirubin despite UDCA administration and are considered inadequate responders [Rudic 2012].

The COMP considered that UDCA is not a satisfactory method for the purpose of this orphan maintenance procedure, as Seladelpar Gilead is intended for a different target patient population, i.e. as second-line treatment option in combination with UDCA, in PBC patients with inadequate response to prior UDCA therapy or as monotherapy in patients unable to tolerate UDCA.

Iqirvo

Iqirvo (Elafibranor) is a dual PPARα/δ agonist. Elafibranor and its main active metabolite GFT1007 are peroxisome proliferator-activated receptor (PPAR) agonists, both of which activate PPAR-alpha, PPAR-gamma, and PPAR-delta in vitro. It stimulates hepatic and muscle beta-oxidation and at the hepatic level it reduces gluconeogenesis and triglyceride production and has an anti-inflammatory effect, promoting a favourable metabolic profile.

Iqirvo is indicated for the *treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.* There is complete overlap with the proposed indication for Seladelpar Gilead.

The COMP considered that there was overlap between Iqirvo and Seladelpar Gilead.

Significant benefit

The sponsor is claiming that their product will offer a clinically relevant advantage over existing authorised therapies as a new therapeutic option to address the life-threatening consequences of PBC and treat PBC-related pruritus. The product can be used in combination with UDCA or in patients

intolerant to UDCA. Scientific advice was sought from the SAWP in 2017 (EMEA/H/SA/3656/1/2017/SME/PR/I) but did not include a question on significant benefit.

A comparison to Iqirvo was submitted to establish significant benefit.

Overview of Significant Benefit Arguments

The sponsor did not provide direct comparison data to elafibranor (Iqirvo) in their submission. They relied on data from their two Phase 3 pivotal studies: CB8025-32048 and ELATIVE to inform a proper assessment of a clinically relevant advantage of seladelpar against elafibranor in the context of maintaining the orphan designation.

In terms of efficacy, the sponsor proposes that seladelpar has demonstrated clinically relevant advantage to elafibranor, and the magnitude of the clinically meaningful effects were established in terms of:

- A clinically meaningful and statistically significant reduction in cholestatic pruritus, a key symptom impacting PBC patients, which was consistent across studies and multiple measures of pruritus.
- ALP normalisation, an increasingly recognised treatment aim.
- Alanine transaminase (ALT) reduction, a marker for liver injury.

In terms of safety, clinically relevant advantage of 10 mg seladelpar over elafibranor was supported in terms of:

- No evidence of increases in blood creatine kinase (CK) or muscle injury, including induction or worsening of myalgia, myopathy, or rhabdomyolysis
- No warning for adverse effects on foetal and newborn development or contraindication in known/suspected pregnancy or in women of childbearing age who do not use contraception
- No adverse events of drug-induced liver injury (DILI) or hypersensitivity reactions attributable to seladelpar.

The sponsor provided a Matched Adjusted Indirect Comparison (MAIC) between seladelpar and elafibranor. This MAIC is summarised below.

The most relevant studies to be used for a MAIC comparison of the efficacy of seladelpar and elafibranor in the treatment of PBC are the respective pivotal studies for each drug:

- Seladelpar: Study CB8025-32048 (RESPONSE) was an international placebo-controlled, randomised, double-blind Phase 3 study to evaluate the efficacy and safety of seladelpar in patients with PBC and an inadequate response or intolerance to UDCA. Subjects were randomised 2:1 to receive placebo or seladelpar 10 mg once daily for 12 months (Hirschfield et al., 2024).
- Elafibranor: The ELATIVE clinical trial was an international placebo-controlled, randomised, double-blind Phase 3 study to evaluate the efficacy and safety of elafibranor in patients with PBC who had an inadequate response or intolerance to UDCA. Subjects were randomised 2:1 to receive elafibranor 80 mg or matching placebo once daily for 12 months. For the purpose of this MAIC analysis, the publicly available aggregate data from the ELATIVE study was used (Kowdley et al., 2023).

These pivotal studies are the most suitable to be used in the proposed indirect MAIC comparison as they are the largest studies performed with the respective drugs, evaluated the dose levels intended to

be used in the clinic (10 mg for seladelpar and 80 mg for elafibranor), and were conducted in the population intended to be treated (PBC patients with an inadequate response or intolerance to UDCA).

As the RESPONSE and ELATIVE studies share the same comparator (placebo, which allows for anchored analysis), include similar target populations, and have identical primary endpoints they are ideal for use in comparison of seladelpar and elafibranor efficacy in the PBC population.

The following baseline variables (Table 6) were available in both the ELATIVE and RESPONSE datasets and were considered of interest as potential matching variables due to their clinical relevance. A rationale for which variable was selected or discarded for matching is presented in this section.

Age, sex, race, duration of PBC, ALP, and total bilirubin were identified as potential confounders or effect modifiers. Data on these variables were available for subjects in both studies and therefore they were selected for matching. UDCA is the standard of care in PBC, with a well-documented effect on disease progression, and therefore its use at baseline was also included for matching populations.

Pruritus was not selected as a matching variable in the main analysis as it is not suspected to be an effect modifier for the primary outcome (biochemical endpoint) as described below. Pruritus was selected as a matching baseline covariate for the secondary pruritus analysis.

Table 1. Potential Variables Considered for Matching

Variable	Statistics	Selected for Matching – Biochemical Endpoints	Selected for Matching – Pruritus Endpoint
Age	Mean, SD	Yes	Yes
Sex	Proportion	Yes	Yes
Race (White)	Proportion	Yes	Yes
Duration of disease	Mean, SD	Yes	Yes
Liver stiffness by transient elastography	Mean, SD	No	No
Pruritus NRS score	Mean, SD	No	Yes
ALP	Mean, SD	Yes	No
Total bilirubin	Mean, SD	Yes	No
AST	Mean, SD	No	No
ALT	Mean, SD	No	No
GGT	Mean, SD	No	No
UDCA use	Proportion	Yes	No

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; NRS = numerical rating scale; SD = standard deviation; UDCA = ursodeoxycholic acid.

Weights were obtained by re-weighting the IPD of RESPONSE to match ELATIVE study baseline summary statistics, as described below. Detailed statistical methods can be found in Signorovitch et al., 2012.

Let x_{ij} be the IPD of RESPONSE, i.e. ith subject's jth select baseline variable, where $i = 1,2,\dots,N, j = 1,2,\dots,K,$ where N is the number of RESPONSE subjects used in the MAIC analysis and K is the number of matching variables. Let $\overline{y}_j$ be the summary statistic of jth select baseline variable in ELATIVE study, e.g. x_{i1} is the age of the ith subject in RESPONSE; $\overline{y}_1$ is the mean age in ELATIVE.

Similar to matching methods based on propensity scores, the weight can be formulated based on the logistic regression model:

$w_i = \mathrm{EXP}\left(\beta_0 + \sum_{j=1}^{K} x_{ij} * \beta_j\right)$,

where β_0 and β_j are unknown parameters.

To have weighted statistics (e.g. mean) of RESPONSE baseline variables match those of ELATIVE, we have equations:

$$\frac{\sum_{i=1}^{N} w_i * x_{ij}}{\sum_{i=1}^{N} w_i} = \frac{\sum_{i=1}^{N} \mathrm{EXP}\left(\beta_0 + \sum_{j=1}^{K} x_{ij} * \beta_j\right) * x_{ij}}{\sum_{i=1}^{N} \mathrm{EXP}\left(\beta_0 + \sum_{j=1}^{K} x_{ij} * \beta_j\right)} = \overline{y}_j$$

Signorovitch et al., 2012 shows that the unknown parameters β_j in the above equations can be estimated by using the generalised method of moments.

Endpoints and Analysis

Biochemical Endpoints

The key efficacy endpoints used for comparison between RESPONSE and ELATIVE are:

- Primary composite biochemical endpoint at Month 12 (ALP <1.67× ULN, ≥ 15% ALP reduction, and total bilirubin ≤ ULN).
- Key secondary endpoint of ALP normalisation at Month 12.

Effect on Pruritus

In addition to the composite biochemical endpoint and ALP normalisation, a comparison of effect on pruritus was also undertaken as a secondary independent MAIC, in order to assess potential benefit regarding pruritus amelioration. Pruritus was not a matching covariable in the primary analysis (as stated above) and was included as a matching variable specifically for the ancillary pruritus analysis only.

Results

Population Matching

The inclusion and exclusion criteria related to liver health for RESPONSE and ELATIVE are comparable, leading to patient characteristics overall conducive to assessing composite biochemical response and associated markers of cholestasis and liver injury across the two studies.

Weights and Effective Sample Size

Biochemical Endpoints

The main biochemical endpoint considered was ALP as presented above.

The weights had a tight range from 0.01 to 5.7 with standard deviation (SD) = 0.87. The majority of weights given are around 1, demonstrating that the populations were similar before the matching process began. This is to be expected given the similarities in inclusion/exclusion criteria and demographics at baseline between the two studies.

The ESS is 109, representing a 57% retention rate.

Secondary Pruritus Analysis

A secondary anchored indirect comparison was performed in order to observe changes in pruritus from baseline to 6 months between RESPONSE and ELATIVE studies.

The weights had a tight range from 0.32 to 1.55 with SD = 0.268, again with the majority of weights given are around 1. Matching on a reduced set of variables ensures a high retention rate, thus ESS for this ancillary comparison was 178 (93% retention rate). This small reduction between original RESPONSE sample size and ESS in the MAIC suggests that the overlap between the RESPONSE and ELATIVE study populations is good and that estimates produced from this model will be stable and valid.

Efficacy Results

Biochemical Endpoints

Table 7 displays the results for the proportion of subjects achieving the biochemical composite endpoint (ALP <1.67× ULN, ≥ 15% ALP reduction, and total bilirubin ≤ ULN) and ALP normalisation at Month 12 before and after matching for baseline characteristics. Matching did not cause any major changes in RESPONSE results compared to 61.7% in the unmatched. This compares favourably with the elafibranor results reported from the ELATIVE study (51% composite endpoint response rate), though the placebo adjusted treatment difference is not statistically significant.

Seladelpar in RESPONSE showed better rates of ALP normalisation than elafibranor in the ELATIVE study. Before matching, the rate of ALP normalisation in the seladelpar 10 mg group was 25.0% compared to 0% in the placebo group. Elafibranor 10 mg demonstrated a 15% ALP normalisation rate, again with 0% ALP normalisation rate in the placebo arm of that study. Comparing the relative efficacy of seladelpar and elafibranor results within the MAIC finds no statistically significant differences between both treatments (p=0.20) (Table 5).

Table 2. Comparison of Key Efficacy Endpoints in RESPONSE (Before and After Matching) and ELATIVE

Endpoint	RESPONSE		RESPONSE – After matching		ELATIVE		Anchored Comparison
	Placebo (N = 65)	**SEL 10 mg (N = 128)**	**Placebo (N = 64)**	**SEL 10 mg (N = 127)**	**Placebo (N = 53)**	**ELA 80 mg (N = 108)**	**ΔSEL – ΔELA Mean (95% CI) p-value**
Composite Endpoint							
Response at Month 12, %	20.0	61.7	25.8	58.8	4	51	
CMH Test p-value		<0.0001		<0.0001		<0.001	
Difference (SE), %				33 (9.325)		47.15 (5.48)	-14.1 (-35.35, 7.05) p=0.19
ALP Normalisation							
Response at Month 12, %	0	25.0		23	0	15	
CMH Test p-value		<0.0001		<0.0001		0.002	

Endpoint	RESPONSE		RESPONSE – After matching		ELATIVE		Anchored Comparison
	Placebo (N = 65)	SEL 10 mg (N = 128)	Placebo (N = 64)	SEL 10 mg (N = 127)	Placebo (N = 53)	ELA 80 mg (N = 108)	ΔSEL – ΔELA Mean (95% CI) p-value
Difference (SE), %				23 (3.81)		15.09 (4.92)	7.9 (-4.29, 20.11) p*=0.20

Abbreviations: ALP = alkaline phosphatase; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ELA = elafibranor; LS = least squares; N = total number of subjects; n = number of subjects in the category; N/A = not available; SD = standard deviation; SE = standard error; SEL = seladelpar
*z-test
Source: CSR CB8025-32048

Secondary Pruritus Analysis

Table 8 below displays the anchored comparison of NRS score at Month 6 and 12 between the RESPONSE and ELATIVE studies. Month 6 and month 12 were the pre-specified timepoints for the assessment of NRS for seladelpar and elafibranor, respectively.

Seladelpar shows a significant reduction of NRS score at Month 6 (LS means difference -1.3) compared to placebo, which is statistically significant (p=0.0130), whereas elafibranor does not show statistical significance of difference of NRS score at Month 6 compared to placebo (LS means difference -0.34, 95% CI: -1.49 to 0.80). Nevertheless, the anchored comparison between seladelpar and elafibranor is not statistically significant (LS means difference -0.97, 95% CI: -2.48 to 0.541, p=0.21).

At Month 12, seladelpar also shows a significant reduction of NRS score (LS means difference -1.5) compared to placebo, which is again statistically significant (p=0.0159). Elafibranor does not show statistical significance at Month 12 compared to placebo (LS means difference -0.78, 95% CI: -1.99 to 0.42). However, the anchored comparison at this later timepoint is also not statistically different (LS means difference -0.74, 95% CI: -2.438 to 0.945, p=0.39).

Table 3. NRS Anchored Comparison Results at Month 6 and 12 (MSPN Set)

	RESPONSE - Original		RESPONSE – After matching		ELA (ELATIVE)		Anchored Comparison
	Placebo (N = 65)	SEL 10 mg (N = 128)	Placebo (N = 64)	SEL 10 mg (N = 127)	Placebo (N = 53)	ELA 80 mg (N = 108)	SEL - ELA
MSPN Set	**n = 23**	**n = 49**	**n = 23**	**n = 48**	**n = 22**	**n = 44**	
NRS at Month 6 (MSPN Set)							
Baseline – Mean (SD)	6.6 (1.44)	6.1 (1.42)	6.5 (1.56)	6.0 (1.48)	6.3 (1.2)	6.2 (1.5)	
Change at Month 6 – Mean (SD)	-1.9 (1.96)	-3.1 (2.07)	-2.0 (2.09)	-3.1 (2.20)			
LS means (SE)	-1.7 (0.41)	-3.2 (0.28)	-1.8 (0.42)	-3.1 (0.28)	−1.26	−1.60	

	RESPONSE - Original		RESPONSE – After matching		ELA (ELATIVE)		Anchored Comparison
	Placebo (N = 65)	**SEL 10 mg (N = 128)**	**Placebo (N = 64)**	**SEL 10 mg (N = 127)**	**Placebo (N = 53)**	**ELA 80 mg (N = 108)**	**SEL - ELA**
LS means difference (SE)		-1.5 (0.50)		-1.3 (0.51) P=0.0130		−0.34 (−1.49,0.80) SE ~ 0.58	-0.97 (-2.480, 0.541) p=0.21
NRS at Month 12 (MSPN Set)							
Change at Month 12 - Mean (SD)	-1.8 (2.01)	-3.4 (2.33)	-1.9 (2.07)	-3.2 (2.51)			
LS means (SD)	-1.5 (0.50)	-3.3 (0.33)	-1.6 (0.51)	-3.1 (0.33)	-1.15	-1.93	
LS means difference (SE)		-1.8 (0.60) P = 0.0036		-1.5 (0.61) P = 0.0159		-0.78 (-1.99, 0.42) P = 0.1970 SE ~0.61	-0.74 (-2.435, 0.945) P = 0.39

Abbreviations: CI = confidence interval; ELA = elafibranor; LS = least squares; N = total number of subjects; n = number of subjects in the category; N/A = not available; SD = standard deviation; SE = standard error; SEL = seladelpar.
*z-test.
Source: CSR CB8025-32048.

The COMP noted that the results of the MAIC did not establish a clinically relevant advantage regarding the primary biomarker endpoint of ALP nor the secondary endpoint of pruritus.

The COMP considered that the sponsor should further elaborate and provide a detailed explanation on the MAIC results of the primary composite endpoint:

•

Claims for a clinically relevant advantage.

- Robust, clinically meaningful and statistically significant reduction in cholestatic pruritus, a key symptom impacting PBC patients, which was consistent across studies and multiple measures of pruritus.

The sponsor has submitted clinical data claiming a statistically significant effect over placebo for cholestatic pruritus, pruritus as measured by pruritus Numerical Rating Scale (NRS) and pruritus as Measured by Patient Questionnaires/Quality of Life Measures. Although a statistically significant effect was clearly established versus placebo for these different parameters the indirect comparative data provided in the submitted MAIC did not establish a clinically relevant advantage between seladelpar and elafibranor.

- ALP normalisation, an increasingly recognised treatment aim.

The sponsor proposes that an unanchored comparison between seladelpar and elafibranor shows a more favourable effect for seladelpar. In CB8025-32048, normalisation of ALP level at Month 12 was observed in 25.0% of the subjects (32 of 128) treated with seladelpar. Evaluation of ALP normalisation at earlier timepoints also showed a higher percentage of subjects in the seladelpar 10 mg arm achieving ALP normalisation compared with the placebo arm, starting as early as Month 1, with treatment effects continuing through Month 12. In ELATIVE, the percentage of subjects with normalisation of the ALP level was consistently higher in the elafibranor group from Week 4 (Month 1) through Week 52 (Month 12) than in the placebo group, with 15% of subjects achieving ALP normalisation at Month 12.

- ALT Reduction

Alanine aminotransferase (ALT) is used to evaluate liver injury, as is aspartate transaminase (AST). Increased ALT is indicative of hepatocyte damage (Lala et al., 2024). In CB8025-32048, postbaseline reductions in ALT levels were greater in the seladelpar arm compared with the placebo arm beginning at Month 3 and continuing through Month 12. At Month 12, LS mean changes from baseline were -12.2 U/L in the seladelpar arm compared with -3.9 U/L in the placebo arm (LS mean difference -8.3, 95% CI: -13.6 to -3.1, p = 0.0020). At Months 3, 6, 9 and 12, p-values were < 0.05 for LS mean differences. In ELATIVE, LS mean change from baseline through Week 52 in ALT was -9.3 U/L (95% CI: -13.4 to -5.1) in the elafibranor group and -5.4 U/L (95% CI: -11.4 to 0.5) in the placebo group. This gave a difference of -3.8 (95% CI: -11.0 to 3.4). The sponsor concludes that seladelpar has demonstrated greater ALT reductions than elafibranor in their respective pivotal studies. This was not confirmed in the MAIC as this parameter was not studied.

Safety Benefits

- No evidence of increases in blood creatine kinase (CK) or muscle injury, including induction or worsening of myalgia, myopathy, or rhabdomyolysis.

The sponsor notes that elevated blood CK and muscle injury is included as a warning in the elafibranor SmPC as these adverse events have been reported in clinical studies with the drug, with myalgia reported as a common side effect (Iqirvo SmPC, 2024). Additionally, they note that clinical data for seladelpar does not show a similar effect. This side effect is not taken in context of the totality of the data nor has been addressed in the MAIC. As limited data for both products regarding safety outcomes is all that exists and postmarketing surveillance data has not been submitted the relevance of these findings remain at best preliminary and not enough for a Maintenance review.

- No warning for adverse effects on foetal and newborn development or contraindication in known/suspected pregnancy or in women of childbearing age who do not use contraception

Statements from the SmPC have been used to compare non-clinical in vivo safety data between elafibranor and seladelpar. The sponsor claims that elafibranor can cause adverse effects on foetal and newborn development as found in non-clinical in vivo data. This has not been reported for seladelpar. This level of safety data is no sufficient to establish a significant benefit.

- No adverse events of drug-induced liver injury (DILI) or hypersensitivity reactions attributable to seladelpar.

The sponsor has noted that DILI has been reported for one patient in the FDA product leaflet. Hepatic abnormalities have been reported for both products in their respective SmPCs. The sponsor has not provided additional safety data such as comparable postmarketing surveillance data or other safety data accumulated during the drug development phase. In addition, this adverse event is not

contextualised within the broader safety profile of both products making the establishment of significant benefit difficult. The sponsor concludes: *The potential for DILI in a population being treated for a liver disease is a concern, one which appears greater in PBC patients using elafibranor than in PBC patients using seladelpar.* This statement further supports the COMPs observation that the safety data is inconclusive.

- Improvement in pruritus (as Measured by Pruritus Numerical Rating Scale (NRS))

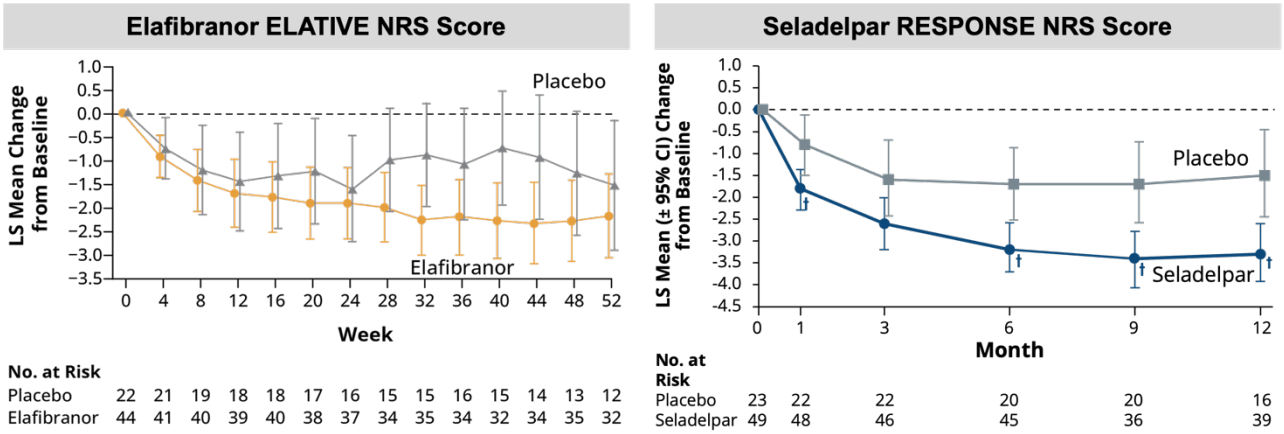
Pruritus NRS, a well-established measure for capturing worst itch (Naegeli et al., 2015; Reich et al., 2016), was used in both seladelpar and elafibranor Phase 3 studies, so comparison between the two studies is possible (Kowdley et al., 2023).

Pruritus NRS has been used in a number of clinical studies with PBC patients (Hegade et al., 2017; Kowdley et al., 2023; Krawczyk et al., 2017). This measure was recommended in scientific advice for seladelpar from the FDA over the use of VAS (where subjects place a mark representing their level of itching since the previous measurement on a 100 mm VAS). An initial study into the experience of PBC patients with pruritus carried out by the Sponsor found that the pruritus NRS was relevant, straightforward and easy to understand in PBC patients, and therefore fit-for-purpose to use in the seladelpar Phase 3 studies (Skalicky et al., 2019). As it is difficult to detect improvement in pruritus in patients that have only mild or no itch, the population best suited to demonstrate a clinically significant improvement in pruritus is the moderate-to-severe pruritus population, made up of patients with pruritus NRS ≥ 4 at baseline, and defined as the MSPN analysis set in CB8025-32048. The same approach was employed in the ELATIVE study.

Pruritus NRS score reduction from baseline was a key secondary objective in both studies. This endpoint was measured at Month 6 in CB8025-32048 and Month 12 (Week 52) in the ELATIVE study.

In study CB8025-32048, treatment with seladelpar led to a statistically significant improvement in pruritus NRS after 6 months compared with placebo in subjects with moderate to severe pruritus at baseline (MSPN population; NRS ≥ 4) (Figure 3, right), and the overall study population. At Month 6, in subjects with NRS ≥ 4 at baseline, the LS mean change from baseline was -3.2 and -1.7 in the seladelpar and placebo arms, respectively (P=0.0047). This effect was sustained through 12 months of treatment (Figure 3, right). In comparison, elafibranor did not significantly reduce pruritus compared to placebo at Month 6 or 12 (Figure 1, left).

Figure 1. Change from Baseline in Weekly Averaged Pruritus NRS Over Time in Subjects with Moderate-to-Severe Pruritus (NRS ≥ 4) at Baseline



Abbreviations: BL = baseline; CI = confidence interval; LS = least squares; M = month; MMRM = mixed-effect model repeated measure; MSPN = moderate-to-severe pruritus NRS; n=number of subjects with non-missing or imputed values at each timepoint; NRS = numerical rating scale.

LS mean change from baseline in the NRS average score (scores range from 0 [no itch] to 10 [worst itch imaginable]) in subjects with moderate-to-severe pruritus over time (NRS score ≥ 4).
Elafibranor (left): Analyses were performed using MMRM, with terms for treatment, visits (4-week periods until Week 52), and treatment-by-visit interaction as fixed factors and with adjustment for baseline NRS values and the stratification factor of ALP > 3x ULN or total bilirubin > ULN. An unstructured correlation matrix was used to model within-subject variability. The NRS scores for subjects who discontinued the trial regimen early or received a rescue therapy for pruritus were considered to be missing data and were handled within the model itself (missing-at-random assumption). Bars indicate 95% CI.
Source: (Kowdley et al., 2023).
Seladelpar (right): MMRM analysis in MSPN analysis set. † $p < 0.05$ versus placebo.
Change from baseline was estimated by the MMRM 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. Bars indicate 95% CI.
Source. CSR CB8025-32048 Table 14.2.5.1 and Table 14.2.9.2

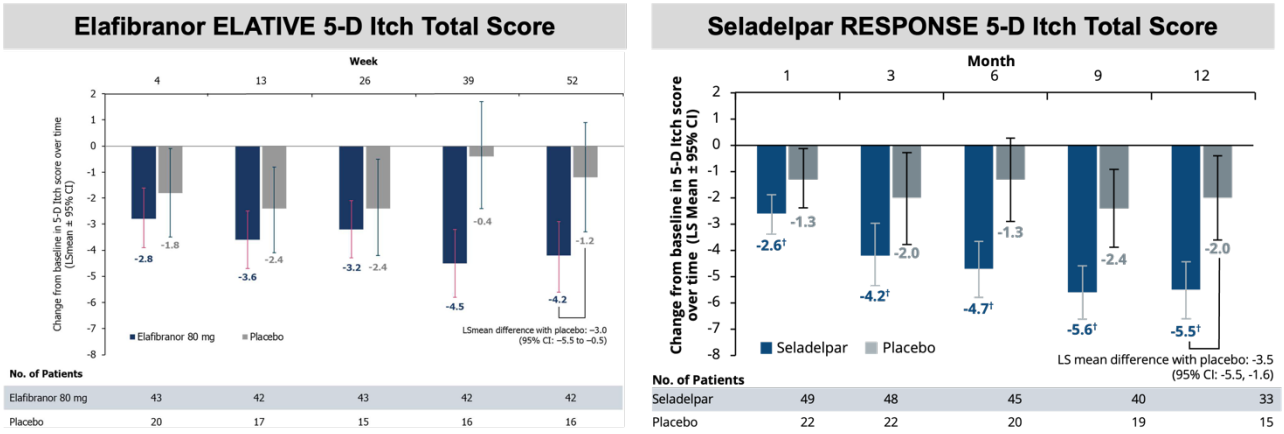
Supportive studies further demonstrated the effect of seladelpar 10 mg in improving pruritus. In the placebo-controlled study CB8025-31735 (ENHANCE), treatment with seladelpar 10 mg led to a statistically significant decrease in pruritus NRS at Month 3 (the primary analysis timepoint). A similar magnitude of reduction in the pruritus NRS was observed in Study CB8025-31731-RE, in an open-label setting. These findings are also supported by reduction in pruritus by the VAS with seladelpar in the earlier, Phase 2 open-label study CB8026-21629.

- Pruritus as Measured by Patient Questionnaires/Quality of Life Measures

The impact of seladelpar on itch and QoL was measured in study CB8025-32048 as secondary and exploratory endpoints using the PBC-40 and 5-D itch scale questionnaires. PBC-40 is a patient-derived, disease-specific QoL measure developed and validated for use in PBC that has been widely applied in practice (Jacoby et al., 2005). It is composed of 6 domains: fatigue, emotional, social, and cognitive function, general symptoms, and itch. The PBC-40 has high PBC patient satisfaction when compared to other HRQoL measures (Jacoby et al., 2005). The 5-D itch scale was designed to measure itching in patients with chronic pruritus, including those with liver diseases (Elman et al., 2010). The 5-D itch scale was found to be a suitable supporting measure for clinical studies by the Sponsor in a prior study as it includes relevant domains important to PBC patients (Skalicky et al., 2019). Inclusion of these questionnaires in study CB8025-32048 ensured that the subjects experiences were captured and measured. Pruritus was also assessed in the elafibranor study ELATIVE via the 5-D itch scale and PBC-40 QoL questionnaire as other secondary endpoints. Study CB8025-32048 and ELATIVE did not include adjustment for multiple comparisons for PBC-40 and 5-D itch scale questionnaires, so these HRQoL measures can be compared between the treatments.

In ELATIVE, the change from baseline to Week 52 appeared to favour elafibranor over placebo for the total score on the 5-D itch scale (least-squares mean difference, −3.0; 95% confidence interval [CI], −5.5 to −0.5) (Kowdley et al., 2023) although lack of a between-group difference through Month 6 suggests an inconclusive effect (Figure 2, left). At Month 9 and Month 12, there was variability in the placebo response that may also have impacted the confidence intervals. Overall, there was not conclusive evidence of a treatment effect. This contrasts with results from study CB8025-32048, where seladelpar treatment led to significantly reduced scores from baseline in the 5-D itch scale compared to the placebo arm at all study timepoints (Figure 2, right). 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, giving a LS mean difference of -3.4 (95% CI: -5.3 to -1.5, p = 0.0007). At Month 12, the LS mean change from baseline in the total score of the 5-D Itch scale was -5.5 in the seladelpar arm compared with -2.0 in the placebo arm (LS mean difference -3.5, 95% CI: -5.5 to -1.6, p = 0.0005).

Figure 2. Change from Baseline in 5-D Itch Total Score Over Time in Subjects with Moderate-to-Severe Pruritus (NRS ≥ 4) at Baseline

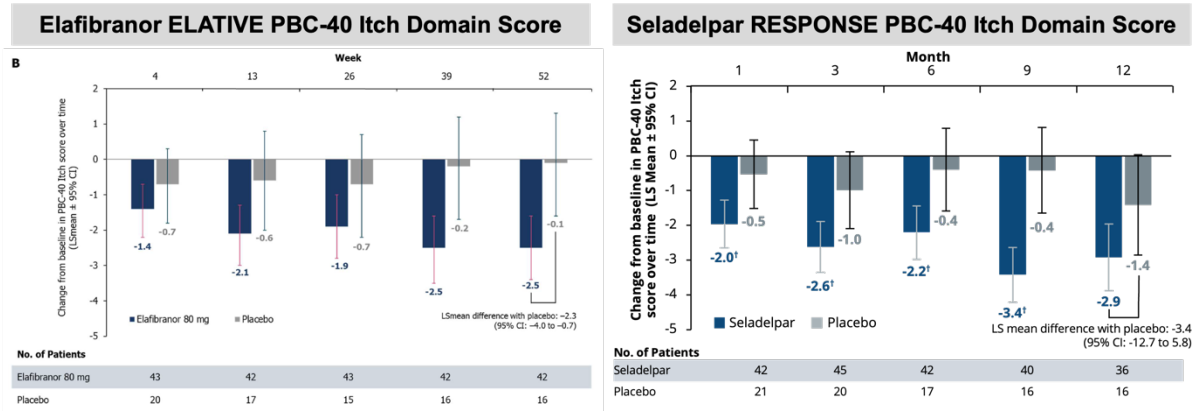


Abbreviations: ALP = alkaline phosphatase; BL = baseline; LS = least squares; M = month; MMRM = mixed-effect model repeated measure; MSPN = moderate-to-severe pruritus; n = number of subjects who had both a baseline value and a value at that timepoint; NRS = numerical rating scale.
5-D Total Score; 5 = no pruritus to 25 = severe pruritus (improvements of pruritus are indicated by lower scores from baseline).
Left: Elafibranor. Analyses used the MMRM with treatment, visits (until Week 52) and treatment-by-visit interaction as fixed factors, and adjusted for baseline values and the stratification factor of ALP >3 times the ULN or total bilirubin above the ULN. Data observed one day or more after subjects stopped treatment prematurely or took a rescue therapy for primary biliary cholangitis were considered as missing data and were handled within the model itself (missing-at-random assumption). Data are presented as LS mean change from baseline±95% CI.
Source: (Kowdley et al., 2023).
Right: Seladelpar. †= p < 0.05 versus placebo; Change from baseline was estimated by the MMRM model including terms for baseline values, 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, and Kenward-Roger correction was applied for the denominator degrees of freedom. Data are presented as LS mean change from baseline±95% CI.
Source: CSR CB8025-32048 Table 14.2.16.1.1.2

Similar results are seen for elafibranor in terms of PBC-40 results. Among the subjects with moderate-to-severe pruritus at baseline, the changes from baseline to Week 52 appeared to favour elafibranor over placebo for the itch domain of the PBC-40 QOL (least-squares mean difference, −2.3; 95% CI, −4.0 to −0.7) (Kowdley et al., 2023); however, an unclear treatment difference through Month 6, with variability in the placebo response, again is inconsistent with a clear effect on symptoms of itch (Figure 5, left). Overall, a pattern of treatment effect with elafibranor may be suggested but is not confirmed.

Consistent with the results demonstrated by the NRS score, as well as the 5-D itch questionnaire, seladelpar demonstrated better results on the itch domain of the PBC-40 QoL questionnaire than elafibranor. Seladelpar led to greater decreases compared to placebo in the PBC-40 itch domain throughout the treatment period, with p < 0.05 for comparisons at Months 1 to 9 (Figure 3, right) versus placebo. LS mean difference from baseline to Month 6 was -1.8 (95% CI -3.22 to -0.39, p=0.0131) for seladelpar. At Month 12, the LS mean difference from baseline was -1.51 (95% CI -3.25 to 0.22, p = 0.0851).

Figure 3. Changes in PBC-40 Itch Domain Score Over Time in Subjects with Moderate-to-Severe Pruritus (NRS ≥ 4) at Baseline



Abbreviations: BL = baseline; CI = confidence interval; LS = least squares; M = month; MSPN = moderate-to-severe pruritus numerical rating scale.
Left: Elafibranor. Analyses used the mixed model for repeated measures with treatment, visits (until Week 52) and treatment-by-visit interaction as fixed factors, and adjusted for baseline values and the stratification factor of alkaline phosphatase >3 times the ULN or total bilirubin above the ULN. Data observed one day or more after subjects stopped treatment prematurely or took a rescue therapy for primary biliary cholangitis were considered as missing data and were handled within the 20 model itself (missing-at-random assumption). Data are presented as LSmean change from baseline±95% CI.
Source: (Kowdley et al., 2023).
Right: Seladelpar. For seladelpar: † $p < 0.05$ vs placebo. Change from baseline was estimated by the MMRM model including terms for baseline PBC 40 QoL score, stratification variable (baseline ALP level < 350 U/L vs ALP level ≥ 350 U/L), treatment arm, visit, and treatment-by-visit interaction. Unstructured covariance structure was applied for the repeated measure and Kenward-Roger correction was applied for the denominator degrees of freedom. Data are presented as LSmean change from baseline±95% CI.
Source: CSR CB8025-32048 Table 14.2.10.1.2.

In their concluding observations the COMP noted that the sponsor had not been able to establish significant benefit over Iqirvo based on the outcome of the MAICs provided. The COMP therefore was of the opinion that the sponsor needed to further elaborate on the MAICs submitted versus Iqirvo. The observations reported for this MAICs did not support naïve comparisons and considerations which have been presented in addition by the sponsor.

Concerning Iqirvo further elaboration should be given regarding the imbalance for the placebo arms. Pruritus, ELF and Liver stiffness were not considered in the MAIC for Iqirvo. Further clarification should be given regarding these parameters.

Justification for the significant benefit observation should be further elaborated where a point estimate below 0 was noted in the MAIC between the RESPONSE study (Seladelpar Gilead) and ELATIVE (Iqirvo).

Finally, the effective sample size (ESS) of 57% is reported for the indirect comparison of the composite endpoint which indicates a lack of overlap across the two study populations between the RESPONSE and ELATIVE studies. The sponsor is asked to provide reasons and to justify why the reported ESS is deemed sufficient. They are also requested to provide the ESS for all reported MAIC analysis.

4. COMP list of issues

Significant benefit

The sponsor should further elaborate on the MAICs submitted versus Iqirvo. ELF and Liver stiffness were not considered in the MAIC for Iqirvo. Further clarification should be given regarding these parameters.

Justification for the significant benefit observation should be further elaborated where a point estimate below 0 was noted in the MAIC between the RESPONSE study (Seladelpar Gilead) and ELATIVE (Iqirvo) where differences were noted to be 33% and 47.15%, respectively, which favours the comparator product.

Finally, the effective sample size (ESS) of 57% is reported for the indirect comparison of the composite endpoint which indicates a lack of overlap across the two study populations between the RESPONSE and ELATIVE studies. The sponsor is asked to provide reasons and to justify why the reported ESS is deemed sufficient. They are also requested to provide the ESS for all reported MAIC analysis.

Comments on sponsor's response to the COMP list of issues

The sponsor provided a written response for the list of questions on significant benefit.

Between the LoQ was issued and the discussion at COMP, the marketing authorization of Ocaliva (OCA) had been revoked officially by the European Commission (EC) and removed from the Union Register of active medicinal products for human use: Union Register of medicinal products - Public health - European Commission. Therefore, elafibranor (Iqirvo) is the only relevant satisfactory methods for the purpose of this procedure.

The sponsor discusses the limitations of the MAIC but considered that key benefits of Seladelpar compared to Iqirvo are apparent based on their respective pivotal studies, in particular higher ALP normalisation rates and pruritus benefit with Seladelpar, but there are limitations to the MAIC analyses in demonstrating these differences quantitatively. In order to prove statistically significant comparative efficacy in favour of Seladelpar, the sample size for both the ALP normalisation and pruritus MAICs would need to be at least twice as large. In this rare disease state, it would be nearly impossible to recruit enough patients to power for these post-hoc analyses at the time of study start. Therefore, the Sponsor maintains that the MAIC is underpowered and cannot be relied upon to determine significant benefit. Rather, the Sponsor places more weight on Seladelpar significantly reducing pruritus in the pivotal RESPONSE study, whereas Iqirvo did not demonstrate this statistically significant effect.

Comparison of the pivotal study for seladelpar (RESPONSE) to elafibranor (ELATIVE) demonstrated benefit of seladelpar. Statistically significant reduction in pruritus with seladelpar vs no difference seen with elafibranor on a prespecified, alpha-controlled endpoint of change in pruritus NRS (highest level of statistical evidence) was reported. Seladelpar Gilead offered a significant benefit for the subset of patients with moderate to severe pruritus. The sponsor highlighted that in the OMR for Iqirvo, the key secondary endpoint of reduction of PBC Worst Itch NRS score was not significantly different from placebo at Week 24 and Week 52 in subjects with moderate to severe pruritus treated with Iqirvo (also highlighted in the Iqirvo SmPC, 2024), thus a benefit on pruritus was not established (Iqirvo SmPC, 2024; Kowdley et al., 2023). Seladelpar Gilead demonstrated reduction in pruritus that was consistent and reproducible. The reduction in pruritus is clinically meaningful, consistent across other measures of itch assessed between Seladelpar Gilead and Iqirvo.

As pruritus is a significant symptom of the condition where there are no effective treatments, the COMP considered the effect of Seladelpar Gilead a clinically relevant advantage to Iqirvo and considered that this was the basis of significant benefit for the basis of maintaining the orphan designation.

COMP discussions

The COMP discussed the written response with particular focus on the data concerning the improved effect on pruritus versus elafibranor. It was accepted that the clinical data from the Phase 3 studies for seladelpar and the subsequent conclusions from the MAIC were sufficient evidence to support the basis of a clinically relevant advantage regarding the effects on pruritus. The oral explanation was cancelled as a result.

COMP conclusions

It was concluded that a clinically relevant advantage regarding pruritus had been established in favour of seladelpar versus elafibranor. The COMP recommended maintaining the orphan designation.

5. COMP position adopted on 13 December 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of primary biliary cholangitis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to pruritus, fatigue, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular carcinoma;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Seladelpar Gilead is of significant benefit to those affected by the orphan condition was supported by data which showed a reduction in cholestatic pruritus in patients with the condition, which beneficially affects quality of life, that has not been demonstrated with currently authorised therapy.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Seladelpar Gilead, seladelpar for treatment of primary biliary cholangitis (EU/3/17/1930) is not removed from the Community Register of Orphan Medicinal Products.