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

Australian Public Assessment Report for IQIRVO

Active ingredient: Elafibranor

Sponsor: Ipsen Pty Ltd

July 2025

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

List of abbreviations 4

IQIRVO (elafibranor) submission 5

Proposed indication 6

The condition 6

Current treatment options 6

Clinical rationale 8

Regulatory status 8

Australian regulatory status 8

International regulatory status 8

Registration timeline 8

Assessment overview 9

Quality evaluation summary 9

Nonclinical evaluation summary 10

Clinical evaluation summary 11

Summary of clinical studies 11

Pharmacology 11

Safety 19

Risk management plan evaluation summary 21

Risk-benefit analysis 21

Indication 21

Efficacy 22

Safety 22

Proposed conditions of registration 22

Conclusions 22

Advisory Committee considerations 23

Assessment outcome 24

Specific conditions of registration 24

Product Information and Consumer Medicines Information 25

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ALP	alkaline phosphatase
AMA	anti-mitochondrial antibodies
ARTG	Australian Register of Therapeutic Goods
AUC_{0-24}	area under the plasma concentration-time curve over 24 hours
C_{max}	maximum concentration
EMA	European Medicines Agency
LLN	Lower limit of normal
NRS	Numeric Rating Scale
OCA	obeticholic acid
PBC	primary biliary cholangitis
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
PPAR	peroxisome proliferator-activated receptor
RMP	Risk management plan
t½	terminal elimination half-life
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	time to maximum concentration
ULN	upper limit of normal

IQIRVO (elafibranor) submission

Type of submission:	New chemical entity
Product name:	IQIRVO
Active ingredient:	elafibranor
Decision:	Approved
Date of decision:	18 March 2025
Approved therapeutic use for the current submission:	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 adults unable to tolerate UDCA.
Date of entry onto ARTG:	25 March 2025
ARTG numbers:	IQIRVO elafibranor 80 mg film-coated tablets bottle (441770)
, *Black Triangle Scheme:*	Yes
Sponsor's name and address:	Ipsen Pty Ltd, 627 Chapel Street, South Yarra, Victoria, 3141
Dose form:	film-coated tablet
Strength:	80 mg
Container:	HDPE bottle with a child-resistant polypropylene closure with integrated desiccant unit.
Pack size:	30 film-coated tablets per bottle
Route of administration:	oral
Dosage:	80 mg once daily For further information regarding dosage refer to the Product Information.
Pregnancy category:	Category D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Proposed indication

This AusPAR describes the submission by Ipsen Pty Ltd (the Sponsor)[1] to register IQIRVO (elafibranor) for the following proposed indication:

> *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 adults unable to tolerate UDCA.*

The condition

Primary biliary cholangitis (PBC) is a rare and chronic, progressive autoimmune liver disease characterised by lymphocytic cholangitis, predominantly affecting females.[2] PBC is often progressive, and patients who are not treated or with an inadequate response to UDCA commonly progress to fibrosis, cirrhosis, liver failure and death unless liver transplant is received.

Clinical practice guidelines suggest a diagnosis of PBC is based on the presence of at least 2 of 3 of the following: An elevated serum alkaline phosphatase (ALP) level greater than 1.5 the upper limit of normal; histologic evidence of chronic, non-suppurative biliary ductal destruction; and presence of anti-mitochondrial antibodies (AMA) at a titre of more than 1:40.[3,4,5]

During development of symptoms, which can occur over many years, patients may develop progressive jaundice, portal hypertension and liver failure. Hepatocellular carcinoma may also develop in advanced stages of PBC. Fat-soluble vitamin malabsorption may occur due to a decrease in biliary secretion of bile acids.[6]

Current treatment options

Currently approved medicines for the treatment of PBC are UDCA, a hydrophilic, non-cytotoxic bile acid and obeticholic acid (OCA), a semi-synthetic analogue of the primary bile acid chenodeoxycholic acid, which selectively activates the nuclear hormone receptor farnesoid X receptor.[7]

Up to 40% of patients treated with UDCA have an inadequate response and remain at high risk of disease progression and have reduced transplant-free survival rates compared to UDCA

[1] A sponsor is a person or company who does one or more of the following: a) exports therapeutic goods from Australia, b) imports therapeutic goods into Australia, c) manufactures therapeutic goods for supply in Australia or d) elsewhere arranges for another party to import, export or manufacture therapeutic goods.

[2] Hirschfield GM, Dyson JK, Alexander GJM, Chapman MH, Collier J, Hübscher S, Patanwala I, Pereira SP, Thain C, Thorburn D, Tiniakos D, Walmsley M, Webster G, Jones DEJ. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. Gut. 2018 Sep;67(9):1568-1594. doi: 10.1136/gutjnl-2017-315259. Epub 2018 Mar 28. PMID: 29593060; PMCID: PMC6109281.

[3] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017 Jul;67(1):145-172. doi: 10.1016/j.jhep.2017.03.022. Epub 2017 Apr 18. PMID: 28427765.

[4] Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology. 2019 Jan;69(1):394-419. doi: 10.1002/hep.30145. Epub 2018 Nov 6. PMID: 30070375.

[5] Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology. 2022 Apr;75(4):1012-1013. doi: 10.1002/hep.32117. Epub 2021 Dec 20. PMID: 34431119.

[6] Lindor KD, 2019.

[7] Hirschfield GM, 2018.

responders. Despite ongoing therapy, 26-44% of patients with ALP >1.67 x ULN (considered to be an important marker of disease activity) progress to liver transplant or death over 15 years.[8,9]

OCA was the only approved second line therapy for the treatment of PBC. It was conditionally approved in 2016 by the USA Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of PBC in combination with UDCA in patients with an inadequate response to treatment with UDCA or as monotherapy in patients who are unable to tolerate UDCA. However, marketing authorisation for OCA was withdrawn in 2024 for both the FDA and EMA due to the results of the post-market approval, randomised controlled clinical trial[10] which was a study requested by the FDA and EMA at the time of conditional approval to confirm the efficacy and safety of OCA.

However, there were potential biases underlying the trial, particularly in the placebo arm-due to inadequate enrolment and retention, the study was under-powered for the primary EMA composite endpoint and the FDA composite endpoint.[11] Additionally, the use of OCA has been associated with exacerbation of pruritus (23% vs. 7% in placebo arms).[12] Lower starting doses are thus recommended due to the increased risk of pruritus and there may be the need for additional bile acid binding resins, antihistamines, dose reduction, reduced dosing frequency or temporary dose interruption. Additionally, OCA is contraindicated for use in patients with compensated cirrhosis with portal hypertension and in patients with decompensation events.

Fibrates have been used off-label for treatment of PBC and have shown some benefit e.g., with bezafibrate.[13]

[8] Lammers WJ, van Buuren HR, Hirschfield GM, Janssen HL, Invernizzi P, Mason AL, Ponsioen CY, Floreani A, Corpechot C, Mayo MJ, Battezzati PM, Parés A, Nevens F, Burroughs AK, Kowdley KV, Trivedi PJ, Kumagi T, Cheung A, Lleo A, Imam MH, Boonstra K, Cazzagon N, Franceschet I, Poupon R, Caballeria L, Pieri G, Kanwar PS, Lindor KD, Hansen BE; Global PBC Study Group. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology. 2014 Dec;147(6):1338-49.e5; quiz e15. doi: 10.1053/j.gastro.2014.08.029. Epub 2014 Aug 23. PMID: 25160979.

[9] Murillo Perez CF, Harms MH, Lindor KD, van Buuren HR, Hirschfield GM, Corpechot C, van der Meer AJ, Feld JJ, Gulamhusein A, Lammers WJ, Ponsioen CY, Carbone M, Mason AL, Mayo MJ, Invernizzi P, Battezzati PM, Floreani A, Lleo A, Nevens F, Kowdley KV, Bruns T, Dalekos GN, Gatselis NK, Thorburn D, Trivedi PJ, Verhelst X, Parés A, Janssen HLA, Hansen BE; GLOBAL PBC Study Group. Goals of Treatment for Improved Survival in Primary Biliary Cholangitis: Treatment Target Should Be Bilirubin Within the Normal Range and Normalization of Alkaline Phosphatase. Am J Gastroenterol. 2020 Jul;115(7):1066-1074. doi: 10.14309/ajg.0000000000000557. PMID: 32618657.

[10] Kowdley KV, Hirschfield GM, Coombs C, Malecha ES, Bessonova L, Li J, Rathnayaka N, Mells G, Jones DE, Trivedi PJ, Hansen BE, Smith R, Wason J, Hiu S, Kareithi DN, Mason AL, Bowlus CL, Muller K, Carbone M, Berenguer M, Milkiewicz P, Adekunle F, Villamil A. COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis With Placebo and External Controls. Am J Gastroenterol. 2025 Feb 1;120(2):390-400. doi: 10.14309/ajg.0000000000003029. Epub 2024 Aug 14. PMID: 39140490; PMCID: PMC11774195.

[11] NHS Health Research Authority. COBALT: Study of Obeticholic Acid in Primary Biliary Cirrhosis. Website: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/cobalt-study-of-obeticholic-acid-in-primary-biliary-cirrhosis/. Accessed 26 November 2024.

[12] Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, Drenth JP, Pockros PJ, Regula J, Beuers U, Trauner M, Jones DE, Floreani A, Hohenester S, Luketic V, Shiffman M, van Erpecum KJ, Vargas V, Vincent C, Hirschfield GM, Shah H, Hansen B, Lindor KD, Marschall HU, Kowdley KV, Hooshmand-Rad R, Marmon T, Sheeron S, Pencek R, MacConell L, Pruzanski M, Shapiro D; POISE Study Group. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016 Aug 18;375(7):631-43. doi: 10.1056/NEJMoa1509840. PMID: 27532829.

[13] Corpechot C, Chazouillères O, Rousseau A, Le Gruyer A, Habersetzer F, Mathurin P, Goria O, Potier P, Minello A, Silvain C, Abergel A, Debette-Gratien M, Larrey D, Roux O, Bronowicki JP, Boursier J, de Ledinghen V, Heurgue-Berlot A, Nguyen-Khac E, Zoulim F, Ollivier-Hourmand I, Zarski JP, Nkontchou G, Lemoinne S, Humbert L, Rainteau D, Lefèvre G, de Chaisemartin L, Chollet-Martin S, Gaouar F, Admane FH, Simon T, Poupon R. A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis. N Engl J Med. 2018 Jun 7;378(23):2171-2181. doi: 10.1056/NEJMoa1714519. PMID: 29874528.

Clinical rationale

Elafibranor and its main active metabolite GFT1007 are dual peroxisome proliferator-activated receptor (PPAR) α/δ agonists. Activation of PPARα is claimed to decrease bile acid (BA) synthesis, increase BA detoxification and modulate BA output resulting in decreased bile toxicity and less injury to cholangiocytes and hepatocytes. Activation of PPARδ also regulates transporters that absorb and secrete bile components, contributing to decreased bile toxicity and improving cholestasis.

Activation of PPARα and PPARδ also have anti-inflammatory effects by acting on different pathways of inflammation, NF-κB and B-cell lymphoma 6 (BCL6) pathways, respectively.

Notably, it is the first in class medicine to treat PBC. Obeticholic acid (OCALIVA, or OCA) has been approved in Australia for the treatment of PBC and is the only currently registered medicine on the ARTG apart from UCDA for the treatment of PBC. OCA is a farnesoid X receptor agonist.

Regulatory status

Australian regulatory status

This product is a new chemical entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies including those of the European Union (submitted 28 September 2023), United States of America (submitted 9 October 2023), United Kingdom (submitted 16 November 2023), Canada (submitted 14 June 2024), Switzerland (submitted 6 May 2024) and Singapore (submitted 26 September 2024).

Registration timeline

Table 2 captures the key steps and dates for this submission.

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

Table 1: Registration timeline for IQIRVO (elafibranor), submission PM-2024-00662-1-1

Description	Date
Submission dossier accepted and evaluation commenced	2 April 2024
Evaluation completed	20 November 2024
Advisory committee meeting	7 February 2025
Registration decision (Outcome)	18 March 2025
Registration in the ARTG completed	25 March 2025
Number of working days from submission dossier acceptance to registration decision*	246 days

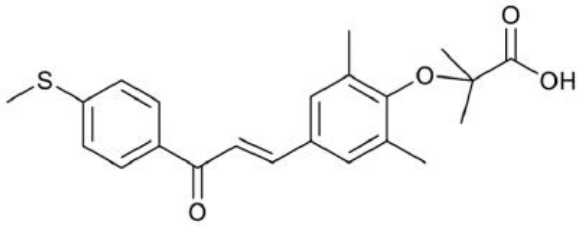
*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

Ipsen Pty Ltd has applied to register IQIRVO (elafibranor) 80 mg elafibranor film-coated tablets. The proposed trade name, IQIRVO, is acceptable.

Figure 1. The chemical structure for elafibranor



There are no British or US pharmacopeial monographs for elafibranor.

Elafibranor is a crystalline powder drug substance that can exist in two polymorphic forms, form A and form B. Form B is found to be more stable and hence, the current manufacturing process manufactures Form B. It is practically insoluble in water at pH 1.2 to 4.5. Hence, the drug substance particle size is controlled using a micronisation procedure in the final drug substance manufacturing step. Particle size limits have been set in line with batches used in the clinical studies.

The elafibranor drug substance manufacturing process is synthesised in four chemical transformations steps.

The proposed specification adequately controls the identity, potency, purity and chemical and physical properties of the drug substance relevant to the dose form. The synthetic impurities are controlled to either ICH Q3A[14] or where higher toxicologically qualified.

The proposed retest period of 60 months when stored at 30 °C is supported by the stability data.

The proposed 80 mg drug product consists of a round, orange film-coated tablet, approximately 8 mm diameter, debossed with “ELA 80” on one side. The excipients used in this formulation are widely used in pharmaceutical preparations and typical for tablet presentations.

The manufacturing process involves wet granulation on a high shear granulation. The manufacturing process appears to have been logically developed and optimised.

The drug product specifications adequately control the quality of the drug product at release and throughout the shelf-life. The impurities are controlled to either ICH Q3B[15] or where higher were toxicologically qualified.

A shelf life of 30 months when stored at 30°C is supported.

The drug product formulation used in the Phase 3 clinical studies is the same as the product formulation proposed for registration. No bridging studies were required.

The Product Information and labelling is considered acceptable from a pharmaceutical quality perspective.

[14] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Q3A (R2) Impurities in new drug substances - Scientific guideline. 2006.

[15] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Q3B (R2) Impurities in new drug products - Scientific guideline. 2006.

There are no objections to registration from a quality perspective.

Nonclinical evaluation summary

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceuticals (ICH M3(R2).[16] The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were GLP compliant. No major deficiencies were identified.

In vitro, elafibranor and its major metabolite GFT1007 were PPAR agonists with a similar selectivity profile on both the human and mice PPAR isoforms. Elafibranor and GFT1007 show a 3.8- and 5.4-fold selectivity for activation of human PPARα over human PPARδ, respectively. The major circulating glucuronidated metabolite racemic GFT3351 and its aglycone precursor, racemic GFT4775, do not contribute to the pharmacological activity of elafibranor. In support of the proposed clinical indication, elafibranor and GFT1007 treatments both prevented the development of macrosteatosis and liver inflammation in a mouse model of non-alcoholic steatohepatitis (NASH). Additionally, elafibranor accelerated reversal of hepatic fibrosis in a rat model of carbon tetrachloride (CCl4)-induced hepatic fibrosis.

No clinically relevant hazards were identified in secondary pharmacology studies.

Safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous systems. No adverse effects were seen on CNS function in rats. Elafibranor had a slight and transient respiratory stimulant action in rats. However, no treatment-related effects on respiratory function were observed in repeat-dose toxicity studies in rats and monkeys at clinically relevant exposures. No significant inhibition of hERG K+ channel tail current by elafibranor or metabolite GFT1007 was observed at clinically relevant concentrations. Elafibranor and metabolite GFT1007 are not predicted to prolong the QT interval in patients.

Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Elafibranor was readily and rapidly absorbed with a similar T_{max} (0.5–2 h) in all species. Plasma protein binding of elafibranor and metabolite GFT1007 was very high (~99.7%) in humans and animal species. Tissue distribution of elafibranor was wide but penetration into brain and spinal cord was limited. No melanin-binding with retention and accumulation was seen in pigmented tissues. Elafibranor was extensively metabolised into GFT1007 in animals and humans. No human-specific metabolites were identified. Elafibranor and metabolite GFT1007 do not undergo major metabolism by the CYP and UGT isoforms. Biotransformation of elafibranor into GFT1007 was partially mediated by the cytosolic enzyme 15-ketoprostaglandin 13-Δ reductase (PTGR1). Drug-related material was excreted predominantly via the faeces in humans and animal species.

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

[16] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals - Scientific guideline. 2013.

Clinical evaluation summary

Summary of clinical studies

The clinical efficacy and safety of elafibranor for the PBC indication was supported by a pivotal phase 3 study (319-1) and a supportive phase 2 study (216-1). 206 patients were included across both studies.

Study 319-1 was a phase 3, randomised, double-blind and placebo-controlled study of 52 weeks followed by (as yet not fully reported) open-label, long-term extension of efficacy and safety of elafibranor 80mg per day in patients with PBC and inadequate response or intolerance to UDCA.

Study 216-1 was a 12 week, phase 2 study of elafibranor 80mg and 120mg vs. placebo in patients with PBC.

Pharmacology

Pharmacokinetics

Following a single oral administration of 80 mg of the to-be-marketed tablet formulation to healthy subjects, the median T_{max} value for both elafibranor and GFT1007 under fasted conditions was 1.50 h, whereas, under fed conditions the T_{max} values were 2.00 and 2.50 h, respectively.

A high fat meal compared to fasting conditions reduced elafibranor C_{max} and $AUC_{0\text{-}t}$ by approximately 48% and 14%, respectively, similarly GFT1007 C_{max} was reduced by approximately 28%, whereas food had no effect on GFT1007 $AUC_{0\text{-}t}$.

Across a single oral dose range of 40 mg to 120 mg, elafibranor and GFT1007 exposure increased in an approximately linear manner with dose.

Across the multi-dose studies, the median elafibranor T_{max} values ranged from 0.50 to 2.00 h, whereas the median GFT1007 T_{max} values ranged from 1.0 to 4.0 h. GFT1007 $AUC_{24,ss}$ values were 2.2- to 5.3-fold higher than for elafibranor. Following multiple QD dosing with 80 mg elafibranor, GFT1007 plasma exposure is approximately 3-fold higher than elafibranor exposure.

Following multiple, oral QD doses of 300 mg or 360 mg elafibranor, steady state of elafibranor was achieved at approximately 14 days and for GFT1007 was achieved within 7 days.

Following administration of a single, oral 80 mg dose of the to-be-marketed tablet formulation under fasted conditions, elafibranor V_d/F was 4731 L.

In vitro studies indicated that both elafibranor and GFT1007 are highly bound to human plasma proteins (>99%), primarily to serum albumin. There was no significant difference in the protein binding of elafibranor and GFT1007 in healthy volunteers and subjects with hepatic impairment or ESRD.

The rapid metabolism of elafibranor due to its active metabolite GFT1007 following oral administration occurs, at least in part, via PGR1. In vitro studies indicate that neither elafibranor nor GFT1007 undergo significant metabolism via CYP P450 or UGT isoforms.

GFT1007 is the major and active circulating metabolite of elafibranor. Isomers of GFT3351 are the other major circulating glucuronide metabolites in humans and are considered pharmacologically inactive.

Following a single oral administration of 120 mg ^{14}C-radiolabelled elafibranor, the plasma exposure of the major metabolites (GFT1007 and GFT3351) was 22-28 higher than that of the parent drug. The mean $t_{1/2}$ values for GFT1007 and GFT3351 were 20.1 h and 8.0 h, respectively and the median T_{max} values for elafibranor, GFT1007 and GFT3351 were 1 h, 1.3 h and 3 h respectively.

Following a 120 mg ^{14}C-radiolabelled dose of elafibranor, 77.1% of radioactivity was excreted via the faeces and approximately 19.3% via the urine.

Following the administration of 120 mg ^{14}C-radiolabelled elafibranor, total radioactivity recovered averaged 96.3%. Ten days after administration, no further radioactivity was detected in expired air, urine or faeces. The total excretion of radioactivity after the first day averaged 30.2% of the administered dose and by Day 7 (144 h post-dose) was 95.6%.

Target population

Plasma concentrations and PK parameters for elafibranor and GFT1007 in subjects with PBC were similar to those measured in healthy volunteers in earlier Phase I studies who were administered comparable dose regimens.

In a reference PBC patient the times to steady state for elafibranor and GFT1007 were 298 h (12.4 days) and 53.4 h (2.22 days), respectively.

Special populations

Compared to healthy subjects, mild, moderate and severe hepatic impairment or ESRD had no clinically significant effects on the PKs of bound elafibranor or GFT1007. Similarly, mild and moderate hepatic impairment had no effect on unbound elafibranor and GFT1007 exposure, whereas severe hepatic impairment increased unbound elafibranor and GFT1007 AUC_t values by 107% and 165%, respectively compared to HS. Therefore, elafibranor is not recommended for use in patients with severe hepatic impairment.

Population pharmacokinetic (PopPK) analysis indicated that age was not a covariate of either elafibranor or GFT1007 PKs.

PopPK analyses indicated that all elafibranor and GFT1007 secondary PK parameters were decreased in patients with relatively higher body weights; however, the effects identified were not expected to be clinically relevant (i.e. changes seen were ~15%).

Elafibranor C_{max} and AUC values were approximately 2- and 1.6- to 1.8-fold higher, respectively, in patients with type 2 diabetes than in overweight or obese participants administered the same dose. By contrast, GFT1007 exposure values were on the whole much more similar between patients with type 2 diabetes and overweight/obese subjects administered 180 mg elafibranor.

Population pharmacokinetics

The final PK model for elafibranor indicated that elafibranor is absorbed via a sequential zero-order and first-order process after a short absorption lag time and its disposition followed a two-compartment kinetic with a linear first-order elimination process. Covariate-parameter relationships identified for elafibranor included: body weight on clearance (CL) and volume of distribution (V) parameters, dose on relative bioavailability (F_{rel}), food on MAT, type of bioanalytical method on individual prediction (IPRED), formulation on relative bioavailability (F_{rel}), zero order input (D1), MAT and lag time to reach the gastrointestinal absorption site (T_{lag}), albumin (ALB) on apparent clearance (CL/F) and apparent inter-compartmental clearance (Q/F), age on apparent peripheral volume of distribution (Vp/F), D1 and $F_{rel,}$ sex on Q/F, BMI on V_p/F, PBC on V_p/F and Study GFT505B-319-1 on T_{lag}.

For elafibranor the bioanalytical method used to determine concentration in plasma had the most prominent effect on PKs (~50% reduction in exposure). Fed subjects had almost 40% lower $C_{max,ss}$ values than fasted subjects.

Covariates that were identified as not having either statistically significant and/or clinically relevant effects on elafibranor PKs included PBC status, age, hepatic and renal impairment and for GFT1007 included: PBC status, age and hepatic impairment.

Drug-drug interactions

There were no effect from statins such as simvastatin and atorvastatin on the PK of elafibranor or vice versa.

The PK of warfarin, R-warfarin and S-warfarin were similar following administration of 15 mg warfarin alone versus warfarin co-administered with 120 mg elafibranor QD.

Steady-state indomethacin 75 mg BD had no effect on the PKs of elafibranor or GFT1007 following a single dose of 120 mg elafibranor.

A single dose of 100 mg sitagliptin did not have a clinically significant effect on the steady-state PKs of either elafibranor or GFT1007 following administration of 100 mg elafibranor QD.

Pharmacodynamics

Mechanism of action

Elafibranor and its equipotent metabolite GFT1007 are PPAR α/δ agonists, which decrease bile acid synthesis, increase bile acid detoxification and modulate bile acid output, resulting in decreased bile toxicity and less injury to cholangiocytes and hepatocytes.

A statistically significant decrease in blood levels of triglycerides was observed following the attainment of elafibranor steady-state, following administration of elafibranor alone (Day 16) or in combination with sitagliptin. It is noted moreover that there were no overall changes in glycaemic or lipid profiles after 52 weeks of elafibranor exposure in the phase 3 pivotal study 319-1.

Pivotal studies

Dosage selection for the pivotal studies

Study 216-1 was a multicentre, double-blind, randomised, placebo-controlled phase 2 study evaluating efficacy and safety of elafibranor 80mg and 120mg after 12 weeks of treatment in patients with PBC and inadequate response to ursodeoxycholic acid.

The primary objective was to evaluate elafibranor 80 and 120mg vs. placebo in subjects with PBC as measured by the relative change from baseline in serum ALP levels.

Secondary objectives were to evaluate efficacy by the multiple endpoints at visit 5 (week 12) including the response to treatment based on composite endpoints (ALP < 1.67 × ULN and TB within normal limit and > 15% decrease in ALP, ALP < 2 × ULN and TB within normal limit and > 40% decrease in ALP).

The study was projected to randomise 45 subjects to 3 treatment groups in a 1:1:1 ratio (elafibranor 80mg, elafibranor 120mg or placebo). 15 subjects in each of the elafibranor arms and placebo arm (45 subjects in total) were estimated to achieve >80% power to detect a percentage difference of -20% in the change from baseline serum ALP for each dose-placebo comparison.

A total of 68 subjects were screened and 45 were randomised. Overall, 45 subjects completed the ITT set with 15 subjects randomised to each of the 3 treatment groups.

For the primary analysis, mean relative change from baseline to endpoint in serum ALP, this was -48.3%, -40.6% and 3.2% for elafibranor 80mg, elafibranor 120mg and placebo, respectively. This revealed statistically significant treatment effect with elafibranor vs. placebo ($p<0.001$). The treatment effect estimate was -52.0% (95% CI [-62.5;-41.5]) for elafibranor 80mg and -43.9% (95% CI [-55.7;-32.1]) for elafibranor 120mg. The majority of subjects in the elafibranor 80mg and 120mg treatment groups had ALP values <1.67 x ULN by week 12 whilst most subjects in the placebo group had ALP values that remained stable and >1.67 x ULN.

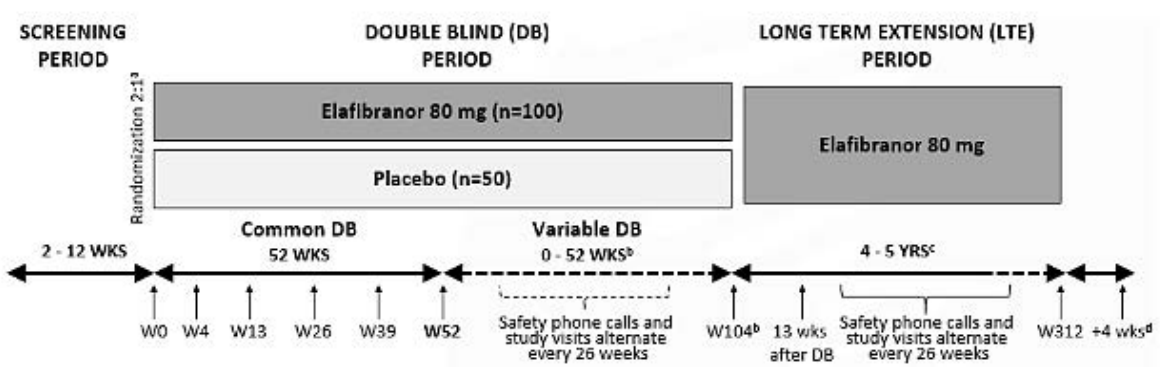
Pivotal study GTF505B-319-1

Study GTF505B-319-1 ("Study 319-1") was a double-blind, randomised, placebo-controlled study, with an open-label long-term extension, evaluating the efficacy and safety of elafibranor 80mg in patients with PBC with inadequate response or intolerance to UDCA.

The current CSR focused on the randomised, double-blind, placebo-controlled component of the study, which included the common double-blind period of 52 weeks and the variable double-blind period of up to an additional 52 weeks. The study initiation date was 24 September 2020 and data cut-off date 01 June 2023. A future report will include data from the entire study including the long-term extension (LTE) period.

Approximately 150 patients were to be randomised in a 2:1 ratio to receive once daily elafibranor 80mg or placebo. Where applicable, patients continued their pre-study dose of UDCA through the study. The study design is shown in Figure 2.

Figure 2. Study GTF505B-319-1 Design



wks—weeks

(a) If receiving UDCA at randomisation. it was continued throughout study participation.

(b) The variable double-blind period was an additional 52 weeks after the end of the common double-blind period (We& 104) or until the last completed Visit 6 (Week 52), whichever occurred first.

(c) The LTE duration will be up to 5 years after end of the double-blind period or until the subject's total treatment duration is 6 years, whichever occurs first.

(d) The safety follow-up period will continue for 4 weeks after last dose of study drug.

Key Inclusion criteria

- Males or females age of 18 to 75 years inclusive at screening visit (SV)1.
- PBC diagnosis as demonstrated by the presence of ≥2 of the following 3 diagnostic criteria:
- History of elevated ALP levels for ≥6 months prior to randomisation (Visit [V]1).

- Positive AMA titres (>1:40 on immunofluorescence or M2 positive by ELISA or positive PBC-specific antinuclear antibody).
- Liver biopsy consistent with PBC.
- ALP ≥1.67 × ULN (based on 2 values).
- Total bilirubin (TB) ≤2 × ULN
- Had at least four available values for PBC Worst Itch Numeric Rating Scale (NRS) score during each of the 7-day intervals in the 14 days prior to randomisation (V1), for a total of at least eight values for PBC Worst Itch NRS score in the last 14 days prior to randomisation (V1).
- UDCA for at least 12 months (stable dose ≥3 months) prior to screening, or unable to tolerate UDCA treatment (no UDCA for ≥3 months) prior to screening.
- If on colchicine, must have been on a stable dose for ≥3 months prior to screening.
- Medications for management of pruritus (e.g. cholestyramine, rifampin, naltrexone or sertraline) must have been on a stable dose for ≥3 months prior to screening.
- Participants taking statins or ezetimibe must have been on a stable dose for ≥2 months prior to screening.

Key exclusion criteria

- History or presence of other concomitant liver disease
- Clinically significant hepatic decompensation, including:
- History of liver transplantation, current placement on a liver transplant list, current MELD-Na score ≥12 linked to hepatic impairment; participants with cirrhosis/portal hypertension complications, including known oesophageal varices, ascites, history of variceal bleeds or related interventions (e.g. insertion of variceal bands or transjugular intrahepatic porto-systemic shunt, and hepatic encephalopathy, history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma); hepatorenal syndrome (type I or II).
- Medical conditions that may cause non-hepatic increases in ALP (e.g. Paget's disease) or which may diminish life expectancy to <2 years, including known cancers.
- Participant had a positive test for human immunodeficiency virus (HIV) Type 1 or 2 at screening, or participant was known to have tested positive for HIV.
- Evidence of any other unstable or untreated clinically significant immunological, endocrine, haematologic, gastrointestinal, neurological, or psychiatric disease as evaluated by the investigator; other clinically significant medical conditions that were not well controlled.
- History of alcohol abuse
- Severely advanced participants according to Rotterdam criteria (TB >ULN and ALB <LLN).
- SV value INR >1.3 due to altered hepatic function.
- SV value creatine phosphokinase (CPK) >2 x ULN.
- Screening serum creatinine >1.5 mg/dL.
- Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as participants with markers of kidney failure damage or eGFR <60 mL/min/1.73 m^2) calculated by Modification of Diet in Renal Disease (MDRD).

- Platelet count <150 x 10^3/μL.
- α-fetoprotein >20 ng/mL, with 4-phase liver computed tomography or magnetic resonance imaging suggesting presence of liver cancer.

Study treatments

Subjects received 1 of elafibranor 80mg tablet or placebo. This was given daily before breakfast with a glass of water. Investigator, participant and study personnel were blinded to treatment and the elafibranor and placebo tablets and packaging were indistinguishable.

Endpoints

The primary endpoint was response to treatment at 52 weeks defined as ALP <1.67 x ULN and TB ≤ULN and ALP decrease ≥15%.

Key secondary endpoints were response to treatment based on ALP normalisation at week 52, change in pruritus from baseline through week 52 based on NRS score and change in pruritus from baseline through week 24 based on NRS score. Other secondary endpoints were change from baseline in ALP at 4, 13, 26, 39 and 52 weeks; ALP categorical responses defined as 10%, 20% and 40% ALP reduction from baseline at week 52 and changes in categories of ALP and bilirubin levels

Randomisation and blinding methods

On completion of screening, eligible patients were randomly assigned to elafibranor 80mg or placebo at the randomisation visit. The randomisation code could be broken by the investigator if urgent action was required for the clinical management of the participant. The list of treatment numbers allocated to each participant was stored in the IXRS (Interactive Voice / Web Response System).

Analysis populations

Subjects with mild and moderately advanced disease were eligible for enrolment while those with advanced cirrhosis and clinical or biochemical evidence of significant hepatic decompensation were excluded. Of those enrolled subjects, those with more advanced disease were identified based on: Rotterdam criteria (bilirubin >ULN or albumin <LLN) for subjects with moderately advanced disease; TB >0.6 x ULN for those at risk of disease progression; liver stiffness measurement (LSM) by transient elastography (TE) >10kPa or Nakanuma fibrosis score 2 or 3 to identify those with advanced fibrosis; and LSM by TE >16.9kPa or Nakanuma fibrosis score of 3 to identify those with cirrhosis (EASL Clinical Practice Guidelines J Hepatol 2009;51(2):237-267).

Sample size

The main analysis for the primary efficacy endpoint used the ITT analysis set and was repeated on the per protocol analysis set. The primary estimand was defined as the OR between treatment groups from all randomised participants and achieving response at week 52 (ALP<1.67 x ULN, total bilirubin ≤ULN and ALP decrease ≥15%) and not stopping the study treatment prematurely or using rescue therapy for PBC.

The assumptions used for determination of the sample size were an expected response rate in the placebo group slightly higher than in the phase 3 pivotal study supporting the regulatory approval of OCA, being ~10%[17] (Nevens et al. 2016); and expected response rate in the elafibranor group at least similar to that seen with OCA (47%).

[17] Nevens, F, 2016.

A total of 150 subjects (100 elafibranor and 50 placebo) was estimated to achieve at least 90% power to demonstrate a statistically significant between-group difference of 35% (47% with elafibranor vs. 12% in the placebo group) in the response rate at week 52 of the primary efficacy endpoint, with a 2-sided α of 0.05, using an exact Fisher test. Assuming 1/50 (2.0%) in the placebo group with ALP normalisation at week 52, 150 participants (100 elafibranor and 50 placebo) provided at least 80% power to detect a statistically significant between-group difference of 20.0% at a 2-sided 0.05 α level.

Assuming a pooled SD of 2.3 points, 60 subjects (40 elafibranor and 20 placebo) with baseline PBC worst itch NRS score >4 provided ~80% power to detect a statistically significant between-group difference of 1.8 points in mean change from baseline in NRS score at a 2-sided 0.05 α level. It was estimated that the same assumptions would apply to the 2 key secondary endpoints for pruritus (through to week 52 and week 24).

Statistical methods

For continuous endpoints, summary statistics of absolute values and absolute/relative changes from baseline were provided. Formal statistical testing was performed on the primary and key secondary endpoints with all tests conducted at the 2-sided, 0.05 level of significance. The fixed-sequence testing approach was used to control the overall type I error rate at a 2-sided 0.05 level. Summary statistics were presented as well as CIs on selected parameters.

The fixed-sequence testing approach implied that if the primary endpoint was statistically significant at a 2-sided 0.05 level, the first key secondary endpoint, ALP normalisation was then tested at the same level. If the first key secondary endpoint was statistically significant at a 2-sided 0.05 level, the second key secondary endpoint (change in pruritus through week 52) was tested at the same level. If this second key secondary endpoint was significant at a 2-sided 0.05 level, the third key secondary endpoint (change in pruritus through to week 24) was tested at the same level. If the primary endpoint was not statistically significant, none of the key secondary endpoints were to be tested. Similarly, if the primary endpoint was significant and the first key secondary endpoint was not significant, the second and third key secondary endpoints were not to be tested and likewise if the second key secondary endpoint was not significant, the third key secondary endpoint was not to be tested.

Participant flow

A total of 94 study centres were selected, 82 identifying and actively recruiting subjects. Of the 244 subjects screened, 83 were screening failures (usually due to eligibility criteria not being met and withdrawal of consent by the subject). Of the 161 randomised subjects (108 to elafibranor and 53 to placebo), 161 were treated and 148 completed the common double-blind period (week 52 of the study).

Results for the primary efficacy outcome

At week 52, the proportion of responders was 55/108 (50.9%) vs. 2/53 (3.8%) in the elafibranor and placebo groups, respectively, with a difference of 47.2% (95% CI: 32.0;56.9) favouring elafibranor. The OR of elafibranor vs. placebo was statistically significant in favour of elafibranor (OR = 37.562 [95% CI: 7.641;302.247]; p<0.0001) (Table 3).

Table 3. Study GTF505B-319-1 Proportion of Participants with Cholestasis Response at Week 52 – Exact CMH Test – Primary Endpoint Main Analysis (ITT Analysis Set).

	Elafibranor 80 mg (N=108)	Placebo (N=53)
Cholestasis response at Week 52, n (%)		
Yes	55 (50.9)	2 (3.8)
No	53 (49.1)	51 (96.2)
No	41 (38.0)	45 (84.9)
No due to ICE	12 (11.1)	6 (11.3)
Proportion of responders	0.509	0.038
95% CI	[0.416; 0.602]	[0.010; 0.128]
Risk difference	0.472	--
95% CI	[0.320; 0.569]	--
Exact CMH		
Odds Ratio of response (elafibranor vs placebo)	37.562	--
95% CI	[7.641; 302.247]	--
p-value	<0.0001	--

CI=confidence interval; CMH=Cohran-Mantel-Haenszel; ICE=intercurrent event; ITT=intent-to-treat

Results for other efficacy outcomes

The response to treatment based on ALP normalisation, the proportion of responders was greater in the elafibranor group vs. placebo (16/108 [14.8%] vs. 0/53 [0.0%] subjects, respectively), resulting in a difference of 14.8% (95% CI: 6.1;22.7) in favour of elafibranor. The OR was significantly in favour of elafibranor (95% CI: 2.786;∞, p=0.0019).

The change in moderate to severe pruritus from baseline through to weeks 52 and week 24 respectively, the LS mean change through week 52 in PBC worst itch NRS score was -1.930 in the elafibranor group and -1.146 in the placebo group, i.e., greater reduction in pruritus with elafibranor, although the LS mean differences between elafibranor and placebo was not significantly different, at -0.784 ([95% CI: -1.986;0.418]; p=0.1970). This lack of difference is shown through to week 52.

There was a rapid reduction in ALP from week 4 that was sustained over 52 weeks of treatment in subjects receiving elafibranor vs. placebo. At week 52, the LS mean (95% CI) change from baseline in ALP was -117.0 U/L (-134.4; -99.6) in the elafibranor 80mg group and -5.3 U/L (-30.4; 19.7) in the placebo group. The LS means difference between groups was -111.7 U/L ([95% CI: -142.0; -81.3; p<0.001). Similar and significant levels of response defined as 10%, 20% or 40% reduction from baseline in ALP were seen in favour of elafibranor vs. placebo, up to 52 weeks.

A greater proportion of subjects treated with elafibranor demonstrated the response to treatment based on ALP <3xULN, AST <2 x ULN and total bilirubin ≤1mg/dL at week 52 vs. those who received placebo. In the elafibranor group, 73/106 (68.9%) showed response vs. 25/53 (47.2%) in the placebo group, resulting in a difference of 22.0% (95% CI: 5.7;37.4), the OR (elafibranor vs. placebo) being 2.852 ([95% CI: 1.339;7.181]; p=0.0061).

Similarly, a greater proportion of participants treated with elafibranor demonstrated the response to treatment based on ALP≤1.5xULN, AST ≤1.5xULN and total bilirubin ≤1mg/dL at week 52 compared to those receiving placebo (43% vs. 5.7% in the elafibranor vs. placebo groups, OR 16.652, p<0.0001).

The proportion of subjects with response to treatment according to a 15% reduction from baseline in total bilirubin at week 52 was likewise greater in the elafibranor group (31.4%) vs. placebo group (22.6%), however the OR did not reach statistical significance at 1.550 ([95% CI: 0.698;3.707]; p=0.3253).

Safety

The safety database presented includes data from the double-blind period of the pivotal Phase 3 study 319-1, and the Phase 2 study 216-1 on PBC. 161 participants with PBC were exposed to elafibranor at the once daily administration of 80mg compared to placebo in study 319-1, while 45 participants with PBC were randomised 1:1:1 to placebo, elafibranor 80 mg, or elafibranor 120 mg. Safety data from participants in other indications who received elafibranor were included.

Overall, a total of 3,745 participants have been enrolled in the elafibranor clinical programme of whom 2,588 have been exposed to elafibranor until the current data cut-off (01 June 2023). Cumulatively, studies conducted in the elafibranor clinical programme since the DIBD have enrolled 3,719 adult participants between 18 to 74 years of age, 16 elderly participants (≥75 years), and 10 paediatric participants between 12 to 17 years.

Treatment emergent adverse events

Treatment emergent adverse events (TEAEs) were reported for 104 (96.3%) subjects in the elafibranor group and 48 (90.6%) in the placebo group. Most TEAEs were mild or moderate in intensity whilst severe TEAEs were seen in 11 (10.2%) and 6 (11.3%) of subjects in the elafibranor and placebo groups, respectively.

TEAEs leading to treatment discontinuation was seen in 11 (10.2%) and 5 (9.4%) subjects in the elafibranor and placebo groups, respectively.

TEAEs reported in >5% of subjects with elafibranor vs. placebo (with a >1% increase in events) were mostly gastrointestinal (vomiting, diarrhoea, nausea, constipation, upper abdominal pain and gastroesophageal reflux disease). There were other numerically increased events with arthralgia and upper respiratory tract infection.

TEAEs reported in >5% of subjects in the elafibranor group with a higher incidence than in the placebo group (difference of >1%), were mostly gastrointestinal in nature, being vomiting (11.1% vs. 1.9%), diarrhoea (11.1% vs. 9.4%), nausea (11.1% vs. 5.7%), constipation (8.3% vs. 1.9%), upper abdominal pain (7.4% vs. 5.7%) and gastro-oesophageal reflux disease (6.5% vs. 1.9%). Other events were arthralgia (8.3% vs. 3.8%) and upper respiratory tract infection (6.5% vs. 3.8%). Corresponding exposure-adjusted incidence rates (subjects per patient-years) [EAIR] for these events however were generally similar between the 2 treatment groups. The only event with a >5% higher incidence in the elafibranor groups vs. placebo group for EAIR difference was vomiting (95% CI: 0.015;0.139).

Subjects receiving elafibranor had numerically fewer TEAEs of pruritus and fatigue vs. placebo, being 20.4% vs. 26.4% for pruritus and 9.3% vs. 13.2% for fatigue, respectively). Other TEAEs reported in >5% of subjects in the placebo group with higher incidence vs. elafibranor were Covid-19 (37.7% vs. 28.7% in placebo vs. elafibranor respectively), UTI (18.9% vs. 11.1%), back pain (11.3% vs. 3.7%), pain in extremity (5.7% vs. 2.8%), muscle spasms (5.7% vs. 2.8%), pain (7.5% vs. 0%), headache (11.3% vs. 8.3%) and hypertension (5.7% vs. 3.7%).

Serious adverse events

Categorisation of TEAEs by severity showed that most events were mild or moderate, there being no severe TEAEs of pruritus or fatigue seen in subjects receiving elafibranor. Severe TEAEs were seen in 11 (10.2%) receiving elafibranor and 6 (11.3%) receiving placebo.

In the open-label, long-term extension period, with 138 subjects entering this period, of whom 45 had received placebo during the double-blind period were analysed. Two of these subjects (all of whom were receiving elafibranor) had serious TEAEs. One had autoimmune hepatitis of moderate intensity leading to subject withdrawal from treatment. Another subject had serious TEAEs of bile duct stone and cholecystitis which were severe in intensity and the study drug was interrupted for these events.

Adverse events of special interest

In terms of adverse events of special interest (AESI), small differences were seen across treatment groups including CPK elevation with no clinically significant differences between treatment groups in the incidence of hyperglycaemia, hypoglycaemia or dyslipidaemia (although as discussed in the efficacy section, there seemed to be more favourable lipid profiles seen with elafibranor treatment).

There were no notable liver biochemistry and hepatic events meeting AESI criteria with elafibranor vs. placebo.

There were no overall differences in haematologic parameters between treatment groups.

There were greater numbers of subjects receiving elafibranor vs. placebo who had serious AEs of renal dysfunction.

There were no clinically significant changes in ECG noted in elafibranor-treated patients compared to placebo.

Vital signs and clinical examination findings

There were no significant changes from baseline in vital signs of clinical significance, with similar assessments seen for elafibranor and placebo groups in the efficacy studies.

Malignancies

None of the seven (6.5%) participants in the elafibranor group and 3 (5.7%) participants in the placebo group who had TEAEs in the system organ class of neoplasms in study 319-1 were considered related to elafibranor.

Creatinine phosphokinase elevations

Four (3.7%) participants in the elafibranor group (and none in the placebo group) had Creatinine phosphokinase (CPK) elevations leading to drug discontinuation in study 319-1. All events were non-serious, and one was moderate in intensity. Three of the 4 cases were assessed as possibly related to study drug. One case was associated to renal impairment. In all cases, the participants had concomitant disease (autoimmune thyroiditis, chronic kidney disease) or concomitant medications (statins) known to be associated with CPK elevations.

Death

There were 2 deaths reported in the elafibranor group due to multiple organ dysfunction syndrome in 1 subject and biliary sepsis and acute kidney injury in the other. None of these were considered related to the study drug.

Risk management plan evaluation summary

Ipsen Pty Ltd has submitted EU-RMP version 1.0 (dated 15 September 2023; DLP 1 June 2023) and ASA version 1.0 (dated 22 February 2024) in support of this application. In its Section 31 response, the sponsor has submitted approved EU-RMP version 1.0 (dated 25 July 2024; DLP 1 June 2023). The ASA was not updated. In its Milestone 5 response, the sponsor has submitted an updated ASA version 1.1 (dated November 2024) in support of its application.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 4.

Table 4. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Hepatic events	ü*	ü†	ü	–
	Myopathy including rhabdomyolysis	ü*	ü†	ü	–
Missing information	Long term safety	ü	ü†	–	–

*Follow up targeted questionnaires

† Studies CLIN-60190-454, GFT505B-319-1 and study CLIN-60190-461

The summary of safety concerns in the ASA is consistent with the approved EU-RMP and is satisfactory.

Routine and additional pharmacovigilance activities are proposed in both the approved EU-RMP and the ASA and they align. The pharmacovigilance plan is satisfactory.

Routine risk minimisation activities only are proposed which is sufficient to manage the safety concerns of this oral medicine.

Risk-benefit analysis

Indication

The indication "for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA" is appropriate, however, the request for elafibranor as "monotherapy in adults unable to tolerate UDCA" is currently not approvable. This is due to the small number of subjects included in the pivotal phase 3 study on elafibranor monotherapy. There were 8 participants in Study 319-1 who received monotherapy at baseline, 6 in the elafibranor group, and 2 in the placebo group. Among the 8 participants, 1 of 6 (16.7%) in the elafibranor group and 0 of 2 participants in the placebo group met the primary efficacy endpoint of cholestasis response. Thus, it is uncertain whether monotherapy alone will have the same magnitude of benefit in a subgroup of patients intolerant of UDCA. However, it is recognised that there is a high unmet need in PBC patients who are intolerant of UDCA.

Efficacy

Study 319-1 is a multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group phase III study followed by an open-label LTE evaluating the efficacy and safety of once daily administration of elafibranor 80 mg in participants with PBC with inadequate response or intolerance to UDCA.

The study achieved the primary endpoint (composite biochemical endpoint i.e. ALP <1.67 x ULN and TB ≤ULN and ALP decrease ≥15%) at Week 52 with 50.9% (55/108) of responders in the elafibranor group compared to 3.8% (2/53) of responders in the placebo group, resulting in a statistically significant estimated difference of 47.2% (95% CI: 32.0; 56.9) favouring the elafibranor group. The estimated OR (elafibranor versus placebo) was statistically significant in favour of elafibranor (OR=37.6 [95% CI: 7.6; 302.2]; p<0.0001). The results are robust as demonstrated by various sensitivity and supplemental analyses. The first key secondary endpoint for ALP normalisation at week 52 also reached statistical significance in favour of elafibranor. However, the second and third key secondary endpoints aimed at evaluating pruritis scores did not reach statistical significance.

While a duration of 1 year was deemed appropriate when discussed with the EMA at the start of the study, the latest EMA guidance recommends a study duration of 2 years.[18]

The primary endpoint was the response to treatment at week 52, defined as a composite biochemical endpoint i.e. ALP <1.67 x ULN and TB ≤ULN and ALP decrease ≥15%. In the latest EMA guidance, the actual clinical relevance of such endpoint and the predictive value on clinical benefit are uncertain.[19]

Safety

The pivotal and supportive studies have demonstrated that the safety profile of elafibranor 80 mg once daily is comparable to that of placebo once daily for a treatment period up to one year. Relevant issues related to the short-term safety profile of elafibranor are gastrointestinal events, possible higher risk of liver events, increased serum creatinine levels and myopathies although no clear causal relationship is evident. The long-term safety profile of elafibranor in PBC patients is yet unknown and the results of the confirmatory study (CLIN-60190-454) would be informative of this aspect.

Proposed conditions of registration

Additional conditions of registration are proposed to support continued approval of elafibranor for the proposed indication:

- The verification and description of benefit with a favourable benefit-risk balance in confirmatory trial(s).

Conclusions

Pending advice from the Advisory Committee for Medicines, I propose to approve the registration of elafibranor for the following indication, subject to conditions as recommended by the clinical and risk management plan evaluators and agreement on an appropriate PI:

[18] European Medicines Agency. Reflection paper on regulatory requirements for the development of medicinal products for primary biliary cholangitis, PBC, and primary sclerosing cholangitis, PSC. 2023.

[19] European Medicines Agency. 2023.

"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".

I am inclined to request a condition of registration for the sponsor to submit the confirmatory study, CLIN-60190-454, upon completion. There are no outstanding concerns from a quality perspective, other than GMP clearance at one manufacturing site.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview,[20] as well as the sponsor's response to these documents, advised the following.

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

There is a small number of subjects included in the pivotal phase 3 study 319-1 on elafibranor monotherapy. There were 8 participants who received monotherapy at baseline, 6 in the elafibranor group, and 2 in the placebo group. Among the 8 participants, 1 of 6 (16.7%) in the elafibranor group and 0 of 2 participants in the placebo group met the primary efficacy endpoint of cholestasis response.

The ACM advised that it would be appropriate for the indication for IQIRVO to include elafibranor monotherapy in adults unable to tolerate UDCA.

While UDCA is generally well tolerated, there is a very small group of patients who are unable to tolerate UDCA due to GI disturbance, paradoxical worsening of pruritus, or allergy. Response to elafibranor would be expected to be similar for UDCA-tolerant patients and UDCA-intolerant patients.

2. ***What is the ACM's viewpoint regarding the usefulness of requesting the sponsor to submit the final results of the confirmatory phase III study (CLIN-60190-454) to the TGA for review upon completion to support continued approval? The confirmatory study has been requested by the EMA and the FDA for elafibranor to attain full marketing authorisation in these jurisdictions (currently granted conditional marketing authorisation only).***

The ACM's viewpoint was that the available efficacy data shows elafibranor as effective in the pivotal phase III clinical trial at improving recognised outcomes in PBC.

The final study report, if requested by the TGA, could be used to update the PI on longer- term adverse events.

The ACM cautioned that CLIN-60190-454 may be affected by issues that contributed to the termination of the COBALT study (see Question 3).

3. ***It is noted that obeticholic acid (approved by the TGA) as second line therapy for the treatment of PBC has recently failed to show significant differences between OCA and placebo in its confirmatory phase III trial, leading to revoking of marketing authorisations in the US and Europe. How does this factor into the ACM's opinion about the potential registration of elafibranor?***

The ACM noted that Questions 2 and 3 each relate to the underlying suitability of the study protocols to confirm the efficacy and safety in PBC of elafibranor (Question 2) and obeticholic acid (Question 3).

[20] A "Delegate" refers to a person within the TGA who has been conferred the authority to make decisions about the approval of therapeutic goods for supply in Australia, under section 25 of the Therapeutic Goods Act.

The COBALT study for obeticholic acid was terminated in part due to:

- lack of clinician and patient willingness to enrol in a study with a placebo arm for a potentially lethal condition
- ability of participants in the placebo arm to identify they were not in the active treatment group and so withdraw from the study.

The ACM cautioned that the confirmatory phase III study (CLIN-60190-454) for elafibranor may be affected by issues that contributed to the termination of the COBALT study.

4. ***What is the ACM's opinion regarding the selection of primary and secondary endpoints for the pivotal phase III trial Study 319-1? It is noted that the latest EMA guidance (EMA/CHMP/299976/2018) states 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. Use of stringent definitions such as complete response has been shown to significantly reduce the placebo response".***

The ACM noted that treatment targets in patients with PBC have evolved significantly over time and have progressively become more stringent. The criteria used in 319-1 were contemporary at the time. More recently, total ALP normalisation has become the treatment goal.

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

The ACM advised that the PI should address the suitability or not of elafibranor in patients with decompensated cirrhosis or cirrhosis with clinically significant portal hypertension; these patients were excluded from the pivotal trial.

ACM conclusion

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

> *"IQIRVO (elafibranor) 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 adults unable to tolerate UDCA"*

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register IQIRVO (elafibranor) for the following indication:

> *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 adults unable to tolerate UDCA.*

Specific conditions of registration

IQIRVO (elafibranor) is to be included in the Black Triangle Scheme. The PI and CMI for IQIRVO must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The IQIRVO EU-Risk Management Plan (RMP) (version 1.0, dated 25 July 2024, data lock point 01 June 2023), with Australian Specific Annex (version 1.1, dated November 2024), included with submission PM-2024-00662-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP).

Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

The final results of the confirmatory phase III study (CLIN-60190-454) should be provided to the TGA when they are available.

Product Information and Consumer Medicines Information

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

Therapeutic Goods Administration

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