25 July 2024
EMA/372188/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Iqirvo

International non-proprietary name: elafibranor

Procedure No. EMEA/H/C/006231/0000

Note

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

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List of abbreviations

ABBREVIATION	Wording definition
5D	5-dimensions
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse events
AESI	Adverse event of special interest
ADR	Adverse drug reaction
AL	Aluminium
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransaminase
AMA	Anti-mitochondrial antibodies
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics classification system
BMI	Body mass index
C4	7-α-hydroxy-4-cholesten-3-1
CEC	Clinical event committee
CFR	Code of federal regulation
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum concentration
CMC	Chemistry, manufacturing, and controls
CKD-EPI	Chronic kidney disease epidemiology collaboration
COSY	Correlation spectroscopy
CPK	Creatine phosphokinase
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
D90	Day 90 safety update
DB	Double-blind

DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DSC	Differential scanning calorimetry
EAIR	Exposure adjusted incidence rate
EASL	European association for the study of liver
EC	European Commission
EMA	European Medicines Agency
EOT	End-of-treatment
ESRD	End stage renal disease
EU	European Union
FDA	Food and Drug Administration
FGF-19	Fibroblast grown factor-19
FMQs	Food and Drug Administration Medical Queries
FT-IR	Fourrier transform infrared spectroscopy
Fu	Unbound fraction
GC-FID	Gas chromatography flame ionization detector
GC-MS	Gas chromatography mass spectrometry
GMP	Good manufacturing practice
HDL-C	High-density lipoprotein cholesterol
HDPE	High density polyethylene
HMBC	Heteronuclear multiple bond correlation
HPIC	High performance ion chromatography
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum coherence
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational new drug
IR	Infrared
ISS	Integrated summary of safety
KF	Karl Fischer titration

kg	Kilogram
kPa	Kilopascals
LDPE	Low density polyethylene
MACE	Major adverse cardiovascular events
MDR1	Multidrug resistance protein 1
MDR2	Multidrug resistance protein 2
mg	Milligram
MO	Major Objection
N°	Number
NASH	Nonalcoholic steatohepatitis
NOAEL	No-observed-adverse-effect level
NDA	New drug application
NMR	Nuclear magnetic resonance
NRS	Numerical rating scale
OCA	Obeticholic acid, Ocaliva®
OATP1B3	Organic anion transporting polypeptide 1B3
PBC	Primary biliary cholangitis
PD	Pharmacodynamic
PDA	Photo diode array
PE	Polyethylene
PgP	P-glycoprotien
PGR1	Prostaglandin reductase 1
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PopPK	Population PK
PPAR	Peroxisome proliferator-activated receptor
PPARα	Peroxisome proliferator-activated receptor alpha
PPARδ	Peroxisome proliferator-activated receptor delta
PPARγ	Peroxisome proliferator-activated receptor gamma
PSC	Primary sclerosing cholangitis
QC	Quality control
QoL	Quality of life

QTPP	Quality target product profile
RH	Relative humidity
RCT	Randomised clinical trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	System organ class
TB	Total bilirubin
TEAE	Treatment-emergent adverse event
TGA	Thermogravimetric analysis
TQT	Thorough QT
UDCA	Ursodeoxycholic acid
UGT	Glucuronosyltransferase
ULN	Upper limit of normal
US	United States
USPI	United States package insert
UV	Ultraviolet
VLDL-C	Very low-density lipoprotein cholesterol
WI	Worst itch
WRO	Written response only
XR(P)D	X-Ray (powder) diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Ipsen Pharma submitted on 9 October 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Iqirvo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004.

Iqirvo, was designated as an orphan medicinal product EU/3/19/2182 on 25 July 2019 in the following condition: primary biliary cholangitis.

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

The applicant applied for the following indication: 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0295/2020 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation / Accelerated assessment

The applicant requested consideration of its application for a conditional marketing authorisation in

accordance with Article 14-a of Regulation (EC) No 726/2004.

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

1.5.2. New active substance status

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

1.6. Protocol assistance

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

Date	Reference	SAWP co-ordinators
17 December 2015	EMEA/H/SA/1342/3/2015/SME/III	*Peter Mol, Elmer Schabel*
17 October 2019	EMEA/H/SA/1342/5/2019/SME/II	*Elmer Schabel, Elina Rönnemaa*
21 July 2022	EMA/SA/0000090534	*Sara Galluzzo, Sheila Killalea*
24 April 2023	EMA/SA/0000119876	*Sif Ormarsdóttir, Elmer Schabel*

The protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Specification and analytical methods for quality control of active substance and drug product; dissolution method including conditions and corresponding limits; comparability of clinical versus commercial drug product batches;
- Adequacy of non-clinical safety data to support phase 3 clinical development;
- Adequacy of early clinical safety data to support phase 3 clinical development; design of phase 3 study in primary biliary cholangitis including eligibility criteria, dose selection, choice of comparator, primary and secondary endpoints, assessment of pruritus via a PRO, statistical considerations (sample size, handling of missing data, control of the type 1 error rate and planned primary and sensitivity analyses), randomisation and stratification factors, safety monitoring and long-term extension; adequacy of primary endpoint to support conditional marketing authorisation; design of a planned phase III/IV confirmatory long-term, placebo-controlled clinical outcomes study (CLIN-60190-454), particularly the primary composite endpoint, the target patient population and eligibility criteria, statistical considerations and methodology and the study duration;
- Orphan similarity aspects.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Paolo Gasparini

The application was received by the EMA on	9 October 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 January 2024
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	29 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 March 2024
The following GCP inspection(s) were requested by the CHMP, and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: A GCP inspection at three site, two investigator sites (UK and Chile) and the sponsor in France between 22 Jan and 15 Mar 2024. The outcome of the inspection carried out was issued on	13 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	06 May 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on	24 May 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 July 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Iqirvo on	25 July 2024
The CHMP adopted a report on similarity on	25 July 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on	25 July 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Iqirvo is proposed to be 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.

PBC is a rare, chronic, progressive autoimmune cholestatic liver disease characterised by lymphocytic cholangitis and associated with increased mortality [Hirschfield 2018]. In untreated patients or those with an inadequate response to UDCA, PBC commonly progresses to fibrosis, cirrhosis, liver failure and death unless a liver transplant is received.

2.1.2. Epidemiology

The estimated prevalence of PBC in North America, Europe, and the Asia-Pacific region varies from 1.91 to 40.2 per 100,000 persons and incidence varies from 0.23 to 5.31 per 100,000 persons, with the incidence of PBC increasing over time in North America and Europe [Lv 2021]. PBC predominantly affects women, with a female to male ratio of approximately 9:1, although lower ratios have been reported in some recent studies [Hirschfield 2021; Webb 2021; Marschall 2019; Yoshida 2018; Boonstra 2014]. PBC is typically diagnosed between 40 and 60 years of age, and global estimates suggest that 1 in 1,000 females aged >40 years are living with PBC [EASL 2017].

2.1.3. Aetiology and pathogenesis

PBC is currently considered an autoimmune disease although recently other factors in the pathogenesis of the disease are suggested. All in all, autoimmunity is an important component of the pathogenesis which is poorly understood.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Approximately 60% of patients with PBC are asymptomatic at the time of diagnosis, often having been referred to a hepatologist for abnormal liver tests, most elevated alkaline phosphatase (ALP) or gamma-glutamyl transferase (γGT) noted at the time of a routine health assessment. Patients may also be diagnosed during laboratory evaluations of non-liver autoimmune diseases (e.g. rheumatoid arthritis, Sjogren syndrome, psoriasis) or investigation of elevated cholesterol or unresolved cholestasis postpartum. Most patients become symptomatic within 10 years of diagnosis [Kumagi 2008]. Initial presentation in symptomatic patients may include fatigue, pruritus, weight loss, right upper quadrant abdominal pain, and sometimes jaundice.

According to practice guidelines (EASL 2017; Lindor 2022; Lindor 2019), a diagnosis of PBC is based on the presence of at least two of three of the following diagnostic criteria: an elevated serum ALP level (>1.5 times the upper limit of normal (ULN)), histologic evidence of chronic nonsuppurative biliary ductal destruction (florid duct lesion), and presence of anti-mitochondrial antibodies (AMA) at a titre of 1:40 or greater [EASL 2017; Lindor 2022; Lindor 2019]. Liver biopsy is generally not required for diagnosis but can be useful in cases where the diagnosis is not clear, such as cases with negative

AMA, or those with features suggestive of concurrent or alternative diagnoses such as autoimmune hepatitis or non-alcoholic steatohepatitis (NASH).

In early PBC, patients are usually asymptomatic despite underlying inflammatory injury of small bile ducts with cholangitis, and slight anomalies in serum liver biochemical tests; this phase may continue for decades [EASL 2017; Montano-Loza 2021]. An intermediate phase of PBC follows, where biochemical abnormalities and clinical symptoms of cholestasis may develop, while underlying lesions progress to ductopenia and liver fibrosis; this phase can continue for up to 10 years or more [Montano-Loza 2021]. In late stage PBC, patients may develop progressive jaundice, portal hypertension, and liver failure, sometimes deteriorating over the span of 2 to 4 years and progressing to liver-related death in the absence of liver transplant. Hepatocellular carcinoma also may develop in advanced stage PBC [EASL 2017; Montano-Loza 2021]. In patients with advanced PBC and jaundice, fat-soluble vitamin malabsorption may occur due to a decrease in biliary secretion of bile acids [Lindor 2019].

In PBC, ALP increases with disease progression, as does bilirubin in more advanced disease, and together are, in clinical practice, both associated with worse long-term clinical outcomes [Lammers 2014]. As PBC advances, ALT and AST may also be elevated due to hepatocellular damage secondary to cholestasis.

Nearly all patients with PBC will become symptomatic during the course of their disease. Pruritus and fatigue are the most frequent symptoms [EASL 2017; Lindor 2019]. Other common symptoms include sicca complex, abdominal pain, arthralgia, restless legs, sleeplessness, depression and cognitive dysfunction.

Pruritus affects up to 70% of patients with PBC and can contribute to substantial morbidity [EASL 2017; Lindor 2019]. Because pruritus follows the circadian rhythm and is often worse at night, patients with PBC may also suffer from diminished sleep quality, leading to increased fatigue and a negatively impacted QoL [Mayo 2023]. Pruritus may occur during early stages of the disease and may continue to persist even in patients with biochemical response or normalisation of ALP following treatment with UDCA.

Fatigue affects up to 80% of patients with PBC, and also negatively affects QoL. Fatigue often interferes with the patient's ability to perform activities of daily living and is characterised by diminished mental and physical capacity [Levy 2023]. While pruritus may improve with liver transplantation, fatigue may persist even after liver transplantation [Carbone 2013].

2.1.5. Management

The only approved medical therapies in the United States (US) and Europe for the treatment of PBC are UDCA, a hydrophilic, noncytotoxic bile acid [Hirschfield 2015; Shi 2006] and obeticholic acid (OCA, Ocaliva), a semi-synthetic analogue of the primary bile acid chenodeoxycholic acid, which selectively activates the nuclear hormone receptor farnesoid X receptor [Hirschfield 2015; UDCA SmPC; UDCA USPI; OCA SmPC; OCA USPI].

UDCA at a daily dose of 13 to 15 mg/kg/day is the only approved first-line therapy for the treatment of PBC [EASL 2017; Lindor 2019]. Treatment with UDCA has been shown to improve liver biomarkers of response, slow disease progression, and improve transplant-free survival [Corpechot 2011]. However, up to 40% of patients treated with UDCA have an inadequate response, and such patients remain at high risk of disease progression and have reduced transplant-free survival rates compared to those classified as UDCA responders. Despite ongoing therapy, 26% to 44% of patients with ALP >1.67 x ULN progress to liver transplant or death over 15 years [Lammers 2014; Murillo-Perez 2020]. Furthermore, treatment with UDCA has not demonstrated an effect on the onset or amelioration of

symptoms, including pruritus or fatigue [Trivella 2023], and it is estimated that between 3% to 5% of patients with PBC are UDCA intolerant [Invernizzi 2017].

OCA is the only approved second-line therapy for the treatment of PBC [EASL 2017, Lindor 2019]. OCA was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2016 for 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 [OCA USPI; OCA SmPC]. However, the efficacy of OCA as second- line therapy is incomplete, with only up to 47% of patients treated with OCA, alone or in combination with UDCA, achieving biochemical response (ALP <1.67 x ULN and ≥15% decrease from baseline and normal total bilirubin levels) compared to 10% treated with placebo, and only 4% achieving ALP normalisation [FDA OCA Review 2016; Nevens 2016]. Furthermore, use of OCA has also been shown to exacerbate pruritus. In a phase III study with OCA, events of severe pruritus were reported in 23% of patients in the OCA 10 mg arm, 19% of patients in the OCA 5 mg to 10 mg arm, and 7% of patients in the placebo arm, while treatment discontinuations due to pruritus occurred more often with OCA than with placebo [Nevens 2016; OCA USPI]. As a result, initiation of OCA at a starting dose of 10 mg once daily is not recommended due to the increased risk of pruritus, and patients with intolerable pruritus due to OCA may need additional management strategies such as bile acid binding resins, antihistamines, dose reduction, reduced dosing frequency, and/or temporary dose interruption [OCA USPI, OCA SmPC]. In addition, post marketing reports in patients treated with OCA [Eaton 2020; Roberts 2020] have restricted its use in patients with PBC and cirrhosis due to reported event of liver injury leading to hepatic decompensation and liver failure [OCA USPI; OCA SmPC].

Fibrates, which are commonly used for the treatment of dyslipidaemia, are used off-label for the treatment of chronic cholestatic diseases such as PBC. Bezafibrate is commonly used off label as a second-line therapy in Europe, while fenofibrate is the most frequently used fibrate in the US. In a randomised, double-blind, placebo-controlled study in 100 patients with PBC and an inadequate response to UDCA, 24 months of treatment with bezafibrate led to a complete biochemical response in 31% of the patients treated with bezafibrate compared to 0% treated with placebo ($p<0.001$) [Corpechot 2018]. Less robust evidence exists to support the use of fenofibrate as a second-line therapy in PBC.

Currently approved therapies for the treatment of PBC have not demonstrated a beneficial effect on the most common symptoms experienced by patients with PBC, pruritus and fatigue. For pruritus, cholestyramine, rifampicin, naltrexone, and sertraline have been recommended in a stepwise approach according to established guidelines [EASL 2017, Lindor 2019]. In a small study of 21 days duration, off-label use of bezafibrate for cholestatic pruritus due to PBC, primary sclerosing cholangitis and secondary sclerosing cholangitis demonstrated greater reduction in moderate to severe pruritus compared to placebo [de Vries 2021], while evidence supporting an anti-pruritic effect for fenofibrate is less robust. For fatigue, despite the significant burden, no effective therapies have been described to date [Levy 2023].

Unmet medical need

Despite the availability of approved medical therapies for PBC, there is a unmet need for additional therapies given the large percentage of non-responders to UDCA at high risk of progression to end stage liver disease, and the limited therapies available to treat the symptoms of pruritus and fatigue that have a major impact on patient QoL.

According to the latest guidelines, those with an inadequate response after 12 months of first line therapy should be considered for second-line therapy due to the increased risk of progressive liver disease [EASL 2017; Lindor 2019]. However, a potential limitation of this step-up approach to patient management is that those at the highest risk of disease progression (i.e. those that do not respond to

first-line therapy) wait the longest to receive effective treatment [Carbone 2018]. The early addition of second-line therapy in patients with an inadequate response to first-line therapy becomes especially important when trying to prevent progression of PBC [Liu 2023].

2.2. About the product

Elafibranor belongs to the pharmacotherapeutic group: Bile and liver therapy, Other drugs for bile therapy. ATC code: A05AX06.

Mechanism of action

Elafibranor and its main active metabolite GFT1007 are dual peroxisome proliferator-activated receptor (PPAR)α/δ agonists.

Activation of PPARα decreases bile acid (BA) synthesis, increases BA detoxification, and modulates 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 this way to decreased bile toxicity and improving cholestasis.

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

Therapeutic indications

Iqirvo is proposed to be 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.

Posology and method of administration

Posology

The recommended dose is 80 mg once daily.

Missed dose
If a dose of elafibranor is missed, the patient should not take the missed dose and instead take their subsequent dose at the next scheduled time point. The patient should not take a double dose to make up for the missed dose.

Elderly patients
No dose adjustment is necessary in patients older than 65 years of age (see section 5.2).

Paediatric population
There is no relevant use of elafibranor in the paediatric population (below 18 years of age) for the indication of PBC.

Renal impairment
No dose adjustment is necessary in patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.
The safety and efficacy of elafibranor have not been established in patients with PBC with severe hepatic impairment. Use in patients with severe hepatic impairment (Child-Pugh C) is not recommended (see section 5.2).

Method of administration

For oral use.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest based on the argumentation and data provided at that stage. This was based on the indirect comparisons against obeticholic acid not allowing for rigorous assessment of an therapeutic advantage and on the data on pruritus that did not demonstrate robust effects.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  The applicant proposes to provide confirmatory/comprehensive data post-authorisation by means of two clinical trials. Elfidence, CLIN-60190-454 is a phase III randomised, parallel-group, double-blind, placebo-controlled, two-arm study to evaluate the efficacy and safety of elafibranor 80 mg on long-term clinical outcomes in adult participants with primary biliary cholangitis (pbc). And study CLIN-60190-461 (elfinity) aims to confirm, among others, the efficacy and safety of elafibranor in a monotherapy setting. This is a prospective, non-interventional, phase IV multicentre study to assess the effectiveness, safety and tolerability of elafibranor 80 mg/day in patients with PBC receiving treatment in a real-world setting.

- Unmet medical needs will be addressed.

  Current treatment options are limited. The only approved medical therapies in Europe for the treatment of PBC are UDCA and obeticholic acid (Ocaliva).

  Treatment with UDCA, the only approved first-line therapy, has been shown to improve liver biochemistry, slow disease progression, and improve transplant-free survival [Corpechot 2005]. However, up to 40% of patients treated with UDCA have an inadequate response [Murillo Perez 2023] and such patients remain at risk of disease progression and have reduced transplant-free survival rates compared to those classified as UDCA responders [Lammers 2014, Kuiper 2009].

  Obeticholic acid is the only approved second-line therapy for the treatment of PBC. The applicant refers to liver-related adverse drug reactions, pruritus, and reduction in HDL-C that have been reported with obeticholic acid and the indication that is restricted for the use of OCA in patients with PBC (with near normal liver function (i.e., Child-Pugh Class B or C) are contraindicated). Further the applicant refers to the frequency of severe pruritus reported in the pivotal study on Ocaliva (23% of patients in the OCA 10 mg arm, 19% of patients in OCA 5-10 mg titration arm, and 7% of patients in the placebo arm). Accordingly, the applicant claims that there remains a significant medical need for new therapies for the treatment of PBC given the percentage of non-responders to UDCA who are at risk of progression to end stage liver disease, the limited therapies available to treat the symptoms of pruritus and fatigue that have a major impact on patient QoLas well as due to the limitations inherent to treatment with OCA in this life threatening disease.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  The applicant claims that this criterion is fulfilled for elafibranor because a high number (40%) of patients remain unresponsive to UDCA and the efficacy and safety limitations of Ocaliva, the

currently only authorised product for second line treatment (see chapter above). The applicant argues that the provided data using well-accepted biomarkers as well as the totality of the data from Study 319-1 and Study 216-1 justify a favourable benefit-risk profile of elafibranor in the claimed indication 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.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 80 mg of elafibranor.

Other ingredients are microcrystalline cellulose, povidone, croscarmellose sodium, anhydrous colloidal silica, magnesium stearate.

Film-coating: polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172), iron oxide red (E172).

The product is available in a high-density polyethylene (HDPE) bottle with a polypropylene child-resistant screw cap with integrated desiccant unit as described in section 6.5 of the SmPC.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of elafibranor is 2-[2,6-dimethyl-4-[(E)-3-(4-methylsulfanylphenyl)-3-oxoprop-enyl]phenoxy]-2-methylpropanoic acid corresponding to the molecular formula $C_{22}H_{24}O_4S$. It has a relative molecular mass of 384.9 g/mol and the following structure:

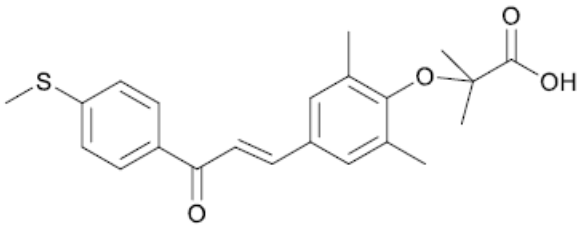


Figure 1: active substance structure

The chemical structure of elafibranor was elucidated by a combination of elemental analysis, NMR (1H, 13C, COSY, 1H- 13C HSQC, 1H- 13C HMBC), mass spectroscopy, UV analysis, and IR spectroscopy. The solid state properties of the active substance were measured by XRPD, dynamic scanning calorimetry (DSC), thermogravimetric analysis (TGA), and Infrared analysis (IR).

The active substance is a powder, and it is non-hygroscopic. It is poorly soluble in water and exhibits pH dependent solubility, the solubility of the active substance increases at higher pH values. The active substance is also micronised to achieve a specific particle size range.

Elafibranor is manufactured as a specific stereoisomer with a trans configuration across the double bond. It can undergo cis-trans isomerisation when in solution and upon exposure to light. The method of analysis in place for the active substance is capable of detecting and separating the isomers.

Polymorphism has been observed for elafibranor. A polymorph screen in various solvent systems identified two potential polymorphic forms. The active substance produced is one of them and is thermodynamically stable. A test is included in the active substance specification for the confirmation of the correct polymorphic form.

2.4.2.2. Manufacture, characterisation and process controls

Elafibranor is synthesised in several main steps using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials, and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in LDPE bags or in an LDPE bag placed inside a heat-sealed LDPE/AL/PE bag, for both of these options the bags are placed in an opaque HDPE drum. The materials comply with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for appearance, identity (FT-IR, HPLC), assay (HPLC), impurities (HPLC, GC-MS), residual solvents (GC-FID, HPIC), water content (KF), residue on ignition (Ph. Eur.), particle size (laser light diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The limits for other impurities are set below the relevant qualification threshold and in line with ICH Q3A requirements.

Where relevant the limits for residual solvents are set in line with ICH Q3C requirements. For one of the solvents no limit is described in ICH Q3C, the applicant has proposed an acceptable limit for this based on toxicological justification.

The active substance synthetic process could lead to the generation of genotoxic impurities. A grouped limit for relevant genotoxic impurities is included in the active substance specifications and the limit for this is appropriately set in line with ICH M7.

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

Batch analysis data for batches analysed throughout the clinical development programme were provided, including three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from seven batches of active substance from the proposed manufacturer were provided, this included four smaller scale batches used in clinical studies and three commercial scale batches stored in the intended commercial packaging for up to 60 months under long term conditions (25 ºC / 60% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. Photostability testing following the ICH Q1B guideline was performed on one batch. Results on stress conditions of acidic, alkali, oxidative, light exposure, along with increased and decreased temperature conditions were also provided on one batch.

The following parameters were tested: appearance, identity (FT-IR, HPLC), assay (HPLC), impurities (HPLC, GC-MS), residual solvents (GC-FID, HPIC), water content (KF), particle size (laser light diffraction), and microbiological quality (Ph. Eur.).

At long term and accelerated conditions all tested parameters were within the specifications, with very little change observed during the studies. The active substance is sensitive to light; however the proposed secondary packaging provides sufficient light protection.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container to protect from light.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is an 80 mg film-coated tablet containing elafibranor. The tablet is round, orange, approximately 8 mm diameter, and debossed with 'ELA 80' on one side.

The aim of development was to generate a suitable formulation for use in the intended population that could also be manufactured at required scale. The Quality target product profile (QTTP) for the proposed product was defined during development and is outlined below.

Table 1: Quality target product profile (QTPP)

QTPP Elements		Target	Justification
Route of administration		Oral	To aid patient acceptability and compliance To achieve required efficacy and safety
Dosage form		Film coated tablet	To aid patient acceptability and compliance Film-coating prevents dust formation during packaging and ensures protection during transportation.
Dosage design		Immediate release	Immediate release design needed to meet label claims
Dosage strength		80 mg	To achieve required efficacy and safety.
Drug product quality attributes	Appearance	Shape, size color and dose identification acceptable to patient	To aid patient acceptability and compliance To allow product identification / differentiation
	Identification	Positive for Elafibranor	To achieve required efficacy and safety

QTPP Elements		Target	Justification
	Assay	Acceptable range	Range set to meet compendial standard, efficacy and safety
	Uniformity of dosage units	Meets pharmacopoeia acceptance criteria	Range set to meet compendial standard, efficacy and safety
	Degradation products	Meets acceptance criteria as per ICH guideline (Q3b)	To meet current standards and safety
	Water content	Meets current specification acceptance criteria	To provide sufficient stability to dosage form
	Dissolution	Meets immediate release tablet formulation characteristics	To meet consistent *in vitro* performance
	Microbial limits	Meets pharmacopeia acceptance criteria	To meet compendial standard and safety
Tablet Mechanical strength		Appropriate tablet hardness.	To withstand coating, packaging, transport and handling
Shelf life		At least 24 months at room temperature	Sufficient stability to meet shelf-life requirements

The active substance is poorly soluble as per BCS criteria, it is a week acid, and its solubility increases at increasing pH conditions. The physical characteristics of the active substance which could have an impact on in-vivo performance are controlled in the active substance specification, where a control for the polymorphic form and the particle size distribution are included.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Relevant functionality related characteristics for the excipients were discussed and are controlled in the relevant excipient specifications where appropriate.

The formulation was developed over the course of the clinical programme. In the early clinical studies various strengths of capsule formulations were used ranging from 5 mg to 60 mg in strength of elafibranor. In the later clinical studies formulations of 80 mg and 120 mg film-coated tablets were developed for use. The commercial formulation for the 80 mg film-coated tablets differs only in the composition of the film-coating as compared to the 80 mg formulation used in the pivotal studies. In the clinical studies a white film-coating was used compared to the orange film-coating used in the 80 mg commercial formulation. The applicant presented in-vitro dissolution profile comparisons to support this change in the film-coating. The profiles were compared using the proposed QC method, and at three pH conditions across the physiological pH range which were pH 1.2, 4.5, and 6.8. The dissolution profiles observed were similar across the tested conditions and support the proposed change to the film-coating.

Different manufacturing processes were investigated during manufacturing process development of tablet formulations. One of the processes was selected as the method of choice and the process was developed at various scale to identify relevant manufacturing parameters and controls.

The discriminatory power of the dissolution method intended for QC testing of the finished product was not originally demonstrated, and the limit proposed was initially not set in line with the performance of the clinical batches. As these aspects could impact the performance of the finished product and the ability of the method to detect relevant changes in dissolution a Major Objection (MO) was raised. This

MO was resolved by the applicant tightening the proposed QC dissolution limit in line with the performance of the clinical batches, and in addition to this the discriminatory power of the dissolution method was demonstrated. The method was shown to be discriminatory with respect to the particle size distribution of the active substance. When the applicant revised the QC dissolution limit in line with the clinical batch performance, data showing compliance with the revised limit was missing from some of the stability studies which impacted the ability to set a shelf-life and appropriate storage conditions for the product, an MO was therefore raised on this aspect. To resolve this remaining aspect the applicant provided additional stability data showing compliance to the revised limit.

The primary packaging is a HDPE bottle with a polypropylene child-resistant screw cap with integrated desiccant unit. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of 10 main steps: dispensing, granulation, wet calibration, drying, dry calibration, pre-mixing, final blending, tabletting, coating, packaging. The process is considered to be a standard manufacturing process.

The level of details included in the manufacturing process description is considered adequate. All critical steps identified during the manufacture of the finished product were listed and are adequately controlled. The identification of steps as critical or non-critical is adequately justified in the dossier. Major steps of the manufacturing process have been evaluated by a number of studies on three commercial scale batches. In addition to this, a process validation scheme has been presented outlining the process validation to be conducted at the proposed manufacturing site. As the process is considered to be standard, the proposal for prospective validation is considered to be acceptable. The proposed bulk holding time of 24 months is acceptable.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description, identification (HPLC-UV, HPLC-PDA), assay (HPLC), degradation products (HPLC), uniformity (Ph. Eur.), dissolution (HPLC), water content (KF), microbiological quality (Ph. Eur.).

The specification parameters are in line with relevant ICH guidelines and proposed limits have been adequately justified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The originally provided nitrosamines risk assessment was not considered sufficient. An MO was raised as the full evaluation report had not been provided demonstrating that all suspected and actual root causes had been taken into consideration in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). To resolve this MO the applicant provided the full evaluation report taking into account the relevant guidance. The information provided was acceptable and outlined that there is no risk for these impurities and therefore no specific control measures are deemed necessary.

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

Batch analysis results are provided for six batches, including three at commercial scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay (HPLC), degradation products (HPLC), dissolution (HPLC), water content (KF), microbiological quality (Ph. Eur.). The analytical procedures used are stability indicating. No significant change was observed during the long term or accelerated studies and the data demonstrates the product is stable at the conditions tested.

In addition, one commercial scale batch was exposed to light as defined in the ICH Guideline on photostability testing of new drug substances and products. The product is not sensitive to light.

With respect to ongoing stability studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 36 months without any specific storage conditions as stated in the SmPC are acceptable.

2.4.3.5. Adventitious agents

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

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure one MO concerning quality aspects was raised, this concerned the initial limit proposed for the QC dissolution test of the finished product, and the discriminatory power of the method for this test. The applicant revised the QC dissolution limit in line with the performance of the clinical batches and substantiated the acceptable discriminatory power of their method. Insufficient information was provided in the response concerning compliance of the stability samples with the revised dissolution method, and an MO was maintained on this aspect. The applicant resolved this by providing the outstanding information, which demonstrated compliance with the revised limit and allowed the setting of an appropriate shelf life and storage conditions.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

Elafibranor is a dual peroxisome proliferator-activated receptor (PPAR)α,δ agonist developed by Ipsen for the treatment of primary biliary cholangitis (PBC). After oral administration, elafibranor is rapidly metabolised in all species to the principal pharmacologically active metabolite GFT1007. The mechanism of action is briefly outlined by the applicant based on a limited number of literature references. In principle, activation of PPARα and PPARδ receptors influences bile acid metabolism, with PPARα reducing synthesis and enhancing detoxification, and PPARδ regulating bile compound transport and absorption, while both exert anti-inflammatory effects via distinct pathways.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The primary pharmacodynamics of elafibranor was evaluated in a series of *in vitro* studies that included PPAR nuclear reporter activation assay, target gene expression analysis and PPARγ property assays.

The ability of elafibranor and its metabolites (GFT1007, GFT1686, GFT1020, GFT1119, GFT1326, GFT1590 and GFT1591) to activate the human and murine PPAR nuclear receptors was assessed in monkey kidney COS-7 cells that were transiently cotransfected with the Gal4 response element (RE)_thymidine kinase (TK)pGL3 reporter plasmid and plasmids coding for the Gal4 deoxyribonucleic acid (DNA) binding domain (DBD) in fusion with the ligand binding domain (LBD) of the human and murine PPAR isoforms. Transfected cells were incubated with various concentrations of elafibranor and its metabolites, with reference ligands (fenofibric acid, rosiglitazone and GW501516) for the different nuclear receptors, or with vehicle (1% dimethyl sulfoxide, DMSO). Elafibranor and its tested metabolites GFT1007, GFT1686, GFT1020, GFT1119, GFT1326, GFT1590 and GFT1591 all activated the 3 PPAR isoforms from the two species with relatively similar profiles. Elafibranor (GFT505) and its main metabolite GFT1007 have comparable profiles and exhibit the same activity on human and murine PPARs. They are both pan PPARα, γ, δ agonists, but more potent on PPARα than on PPARγ and PPARδ. Compared to reference agonists, elafibranor and GFT1007 act on the three PPAR isotypes as partial agonists. On human PPAR isoforms, the EC_{50} values of elafibranor are 0.046, 0.143 and 0.177 respectively for PPARα, γ, δ. Elafibranor exhibits approximately a 3 or 3,8 -fold more potent activity on PPARα than on PPARγ and PPARδ. On murine PPAR isoforms, the EC_{50} values of the elafibranor are 0.054, 0.142 and 0.336 respectively for PPARα, γ, δ. Elafibranor exhibits approximately a 2,6 or 6,2-fold more potent activity on PPARα than on PPARγ and PPARδ. GFT1007 exhibits approximately a 7,6

(7,1) or 5,4 (11,7) more potent activity on PPARα than on PPARγ and PPARδ on human or murine PPAR isoforms.

Elafibranor is rapidly metabolised in all species to the metabolite GFT1007. Further metabolism of GFT1007 leads to the formation of the acyl glucuronide metabolite GFT3351, that exists in 4 stereoisomeric forms. The metabolite GFT4775 also exists in 4 stereoisomeric forms that represent the aglycone precursors of the 4 stereoisomeric forms of GFT3351. In order to determine whether they contribute to the pharmacological activity of elafibranor, their ability to activate PPARs were evaluated. In the *in vitro* PPAR nuclear reporter activation assay, racemic GFT3351 showed no pharmacological activity on any of the PPAR isoforms. Racemic GFT4775 showed limited pharmacological activity on PPAR isoforms (a 400- and 14-fold weaker pharmacological activity as compared to elafibranor on human PPARα and PPARγ, respectively and no activity on PPARδ). Therefore, it can be concluded that GFT3351 and GFT4775 isomers do not significantly contribute to the pharmacological activity of elafibranor.

Elafibranor and its principal active metabolite, GFT1007, were studied for their effects on gene expression in hepatocytes from mouse, rat and human, and compared to reference compounds or vehicle. Hepatocytes from the three species were treated with compounds for 24 hours and the expression of PPAR target genes involved in mitochondrial metabolism and peroxisomal fatty acid oxidation was determined by quantitative reverse transcriptase-polymerase chain reaction (Q-RT-PCR) analysis. In human hepatocytes, elafibranor and GFT1007 induced a significant increase in the expression of the mitochondrial genes pyruvate dehydrogenase kinase 4 (PDK4, 20-70 fold versus control depending on the cell line) and carnitine palmitoyltransferase 1A (CPT1A, up to 8-fold depending on the cell line). In human HepG2 cell lines, this effect was likely via PPARδ activation, since similar effects were observed with the prototypical PPARδ agonist GW501516. In human IHH cell lines, the mechanism was not clear, since comparable effects were observed with all three prototypical PPAR agonists. Elafibranor and GFT1007 effects on the expression of the peroxisomal genes acyl-coenzyme A (CoA) oxidase 1 (ACOX1) and enoyl-CoA hydratase/3-hydroxyacyl CoA dehydrogenase (EHHADH) in human cells were slight and at the lowest dose, and it was not clear via which route this effect was occurring. In rodent hepatocytes, elafibranor and GFT1007 significantly induced the expression of both mitochondrial and peroxisomal genes, likely via PPARα activation, since similar effects were observed with the prototypical PPAR alpha agonist fenofibric acid. The amplitude of the increase in mitochondrial gene expression (PDK4, CPT1A) induced by elafibranor and GFT1007 was significantly greater in human cells than in rodent cells.

The PPARγ properties of elafibranor and its metabolites GFT1007, GFT1590 and GFT1591 were evaluated using 3T3-L1 murine pre-adipocytes or human visceral white pre-adipocytes (HWPv). The PPARγ reference compound (rosiglitazone) stimulated the triglycerides accumulation and adiponectin secretion in the adipocytes in a dose-dependent manner (from 0.001µM). The treatment of 3T3-L1 murine adipocytes or HWPv with the GFT compounds (GFT505, GFT1007, GFT1590 and GFT1591) induced a similar effect to the reference compound, indicating their *in vitro* PPARγ activity. GFT505, GFT1007 and GFT1591 demonstrated a similar efficacy and potency. All three were less efficient than rosiglitazone, whose EC_{50} was at least one log lower. In contrast, GFT1590 appeared to be as efficient and potent as rosiglitazone.

To summarize, the *in vitro* studies show that elafibranor and its principal active metabolite, GFT1007, are both pan PPAR agonists with a similar selectivity profile on both the human and murine PPAR isoforms. They show more potent activity on PPARα than on PPARγ and PPARδ. And compared to reference agonists, elafibranor and GFT1007 act on the three PPAR isotypes as partial agonists. Unlike GFT1007, the major circulating glucuronidated metabolite racemic GFT3351 and its aglycone precursor, racemic GFT4775, do not significantly contribute to the pharmacological activity of elafibranor. In human hepatocytes, elafibranor and GFT1007 both induced the expression of

mitochondrial genes (PDK4, CPT1A), likely via PPARδ activation. However, they had slight effect on the expression of peroxisomal genes (ACOX1, EHHADH), and it was not clear via which route. In rodent hepatocytes, elafibranor and GFT1007 significantly induced the expression of both mitochondrial and peroxisomal genes, likely via PPARα activation. Elafibranor (and its metabolites) induced an increase in intracellular triglyceride content and adiponectin in human and murine adipocytes, indicating their *in vitro* PPARγ activity.

Due to the absence of an animal model that adequately mimics the pathophysiology of human primary biliary cholangitis (PBC), the pharmacological effects of elafibranor have been studied in rodent models of NASH (characterized by liver inflammation and fibrosis, relevant to PBC) and chemically induced liver fibrosis. Elafibranor was evaluated for PPARγ-related side-effects also *in vivo*.

Elafibranor and its metabolite GFT1007 were evaluated for their ability to prevent the development of NASH in genetically diabetic and obese db/db mice fed an MCD diet. Results showed that Elafibranor treatment in MCD diet-fed mice demonstrated dose-dependent reductions in intrahepatic cholesterol and triglyceride content, plasma ALT activity, relative liver weight (liver/brain weight ratio). Microscopic examination confirmed that elafibranor treatment prevented MCD diet-induced steatosis and inflammatory cell foci in a dose-dependent manner. The mild MCD diet-induced liver fibrosis also tended to be reduced by parallel elafibranor treatment. For all hepatic and plasmatic parameters, as well as liver histological findings, the metabolite GFT1007 at 8 mg/kg/day showed a similar efficacy to elafibranor at 9 mg/kg/day. Both elafibranor and GFT1007 tended to reduce the hepatic expression of several proinflammatory and profibrotic genes, in particular tumour necrosis factor α (TNFα), interleukin-1β (IL-1β), collagens and lumican, in keeping with their liver-protective effects.

Liver-protective effects of elafibranor have also been demonstrated in a rat model of carbon tetrachloride (CCl_4)-induced hepatic fibrosis. Results showed that repeated CCl_4 injections in Sprague-Dawley rats over two weeks led to liver damage, early fibrosis, elevated plasma ALT and AST levels, and increased hepatic collagen content, as confirmed by transcriptomic analyses showing upregulation of profibrotic markers such as TGFβ1, collagens, and αSMA, while the expression of inflammatory markers IL-1β and TNFα remained unaffected. Elafibranor treatment for four weeks at 30 mg/kg/day resulted in regression of liver pathology, evidenced by reduced ALT and AST plasma levels, hepatic collagen content, and halted progression of fibrosis and macro- / microsteatosis. Additionally, elafibranor significantly inhibited hepatic inflammatory and profibrotic markers, surpassing expression levels in both control and pre-treatment CCl_4-injected rats.

Elafibranor was evaluated for *in vivo* PPARγ-related side-effects, by determining the effect of oral elafibranor administration on body weight gain and haematocrit in C57BL/6J mice and Sprague-Dawley rats at 10, 100 and 300 mg/kg/day. PPARγ agonist rosiglitazone induced dose dependent weight gain and haematocrit decrease in both mice and rats. No effects were observed with elafibranor in mice. Similarly, elafibranor did not induce body weight gain in rats at any dose but was associated with decreased haematocrit after 11 days of administration at all doses, suggesting a delayed haemodilution effect.

2.5.2.2. Secondary pharmacodynamic studies

Off target activity of elafibranor and its metabolites were tested on 13 nuclear receptors as well as on an extensive panel of enzyme assays and radioligand binding assays. Their inhibitory effects on an extensive panel of recombinant protein kinases were evaluated across 4 *in vitro* studies.

The off-target activity of elafibranor on 13 nuclear receptors other than PPARs was evaluated at concentration from 0.001 to 10 µM. Elafibranor did not activate any of the tested nuclear receptors, PXR, estrogen receptor α (ERα), mineralocorticoid receptor (MR), progesterone receptor (PR),

farnesoid X receptor (FXR), liver X receptor α (LXRα), liver X receptor β (LXRβ). Elafibranor also did not activate these orphan receptors (no reference ligands): CAR, hepatocyte nuclear factor (HNF4), steroidogenic factor-1 (SF-1), estrogen related receptor (ERR), retinoic acid-related orphan receptor (ROR) and liver receptor homolog (LRH), indicating that it specifically activates the PPAR nuclear receptors.

Elafibranor and its metabolites GFT1007, GFT1686, GFT1020, GFT1119 and GFT1326 were tested at 10 µM for off-target effects on an extensive panel of enzyme assays and radioligand binding assays across 6 *in vitro* studies. Results showed that the tested compounds did not exhibit activity on any of the targets evaluated, except for the minor metabolite GFT1326 that showed a 62% inhibition of the human adrenergic α2A receptor.

Elafibranor and its principal active metabolite GFT1007 were tested at 10 µM for inhibitory effects on an extensive panel of recombinant protein kinases across 4 *in vitro* studies. In study one, elafibranor and GFT1007 at 10µM showed no inhibitory potency against TGFβR1 and TGFβR2, suggesting the mechanism of action of these compounds in addressing fibrotic diseases may not involve direct inhibition of TGFβ1 receptor kinase activity. In study two, elafibranor at 10µM showed a significant inhibition of 3/9 tyrosine kinases: PDGFRβ, VEGFR1 and VEGFR2, but not for ABL1, b-Raf, EGFR, JAK2, PDGFRα and VEGFR3. In study three, elafibranor showed a strong inhibition of 4/ 15 tyrosine kinases: FGF-R2, KIT, PDGFRβ and VEGFR2. In contrast, GFT1007, showed no significant inhibition of the 15 protein kinases tested. Elafibranor appears to be a multiple kinase inhibitor, with higher selectivity than Sorafenib but less potency. In study four, Elafibranor inhibited by >50% the kinase activity of 24 /300 wild-type protein kinases tested including tyrosine and Serine/Threonine Kinase.

Elafibranor was tested at concentrations 3 nM to 100 µM to determine the half-maximal inhibitory concentration (IC50) for 20 selected recombinant protein kinases across two studies. Elafibranor showed inhibition of all the tested protein kinases but was less potent than sorafenib (reference compound) for 6/7 tested protein kinases except FGF-R4, indicating that elafibranor is a multiple kinase inhibitor with lower potency than sorafenib.

The mode of action of elafibranor inhibition of PDGFRβ was determined in a biochemical dose-response assay. Elafibranor at 30 µM caused a significant, 5.15-fold increase in the K_M [ATP] for PDGFRβ. The V_{max} of PDGFRβ was decreased by a factor of 2.25-fold by elafibranor at this concentration. Based on the data obtained, the mode of action of elafibranor was classified as mostly ATP-competitive, with a tendency to intermediate.

To summarise, elafibranor showed no activity when screened against a panel of 13 nuclear receptors indicating its specific activation limited to the PPAR nuclear receptors. Elafibranor and its metabolites did not exhibit activity to a large number of receptors, channels, transporters and CYPs, except for the minor metabolite GFT1326 that inhibited the human adrenergic α2A receptor. Elafibranor but not its principal active metabolite GFT1007 was found to be a multiple but selective protein kinase inhibitor. It did not show inhibitory potency against TGFβR1 and TGFβR2, but significantly inhibited several tyrosine kinases such PDGFRβ, VEGFR1 and VEGFR2 as well as some Serine/Threonine Kinase.

2.5.2.3. Safety pharmacology programme

The *in vitro* safety pharmacology programme evaluated the effects of elafibranor and its main metabolits on hERG tail current.

The effect of elafibranor and its main metabolites GFT1007 on hERG tail current was measured by the patch clamp technique in six HEK-293 cells stably transfected with hERG cDNA. At 10 µM, elafibranor produced a slight 20% inhibition of hERG tail current, GFT1007 showed no inhibition.

The *in vivo* elafibranor safety pharmacology program evaluated the effects of elafibranor to cardiovascular function, respiratory or central nervous systems.

The effects of elafibranor on cardiac function were evaluated in a GLP-compliant study after single oral administration to conscious dogs. At all tested doses (30, 100, 300 and 1000 mg/kg), elafibranor did not induce any statistically significant changes in mean, systolic or diastolic arterial pressure. Elafibranor induced a statistically significant and dose-dependent (in terms of duration) increase in heart rate from 100mg/kg. The time of onset was dependent on the administered dose and persisted up to the end of the 24-hour observation period. The cardiac conduction times (PR, PQ interval and QRS complex durations) were slightly but not statistically significantly reduced by elafibranor. Once corrected for heart rate using Bazett's and Fridericia's formulas plus Sarma's method, the QT interval duration was not significantly modified. No disturbance in the ECG (lead II) and no change in the T wave morphology attributable to elafibranor was observed at any dose level. To summarize, except tachycardia was found related to elafibranor treatment from 100 mg/kg, the other cardiac function parameters including mean, systolic or diastolic arterial pressure, cardiac conduction times (PR, PQ, QT intervals and QRS complex), ECG, T wave morphology were not influenced by the elafibranor treatment. The no observed adverse effect level (NOAEL) of elafibranor on cardiovascular parameters in conscious dogs corresponds to 30 mg/kg when administered orally. Thorough QT (TQT) analysis in healthy volunteers excluded any prolongation effect of elafibranor on QT/corrected QT (QTc) interval at repeat doses of up to 300 mg for 14 days. In clinical studies, no clinically meaningful changes in vital signs or in electrocardiogram (ECG) (including QTc interval) were observed in participants treated with elafibranor.

The potential neurobehavioural and body temperature effects of elafibranor using an Irwin observation battery, were evaluated in a GLP-compliant study, after single oral administration (30, 300 and 1000 mg/kg) to male Sprague-Dawley rats. Elafibranor-related adverse effect at any dose level was not found in this study, the NOAEL for neurobehavioural and body temperature effects was 1000 mg/kg (the highest dose tested). It can be concluded that elafibranor has no side effects for central nervous systems at any tested doses.

The effect of elafibranor on respiratory parameters (respiratory rate, peak inspiratory and expiratory flows, inspiration and expiration times, airway resistance index, tidal volume and minute volume) was assessed by the whole-body plethysmography method following oral administration (30, 300 and 1000 mg/kg) in the conscious rats. Elafibranor at the doses of 30 and 300 mg/kg had no effect on respiratory function. At the dose of 1000 mg/kg, elafibranor induced significant increases in peak inspiratory flow at 30 minutes after dosing and in tidal volume at 30 and 60 minutes after dosing, suggesting a respiratory stimulant action. Thus, the NOAEL on respiratory parameters in conscious rats was 300 mg/kg.

2.5.2.4. Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were performed with elafibranor. This is agreed by the CHMP.

2.5.3. Pharmacokinetics

The pharmacokinetic (PK) properties of elafibranor and its major active metabolite GFT1007 have been evaluated in rodents and non-rodents following intravenous (IV) and oral administration. Single-dose administration by IV and oral routes was performed in rat, dog, monkey and minipig. Repeat-dose administration by the oral route was performed in rats, dogs and monkeys during regulatory rodent and non-rodent toxicity studies. Metabolite profile was investigated in liver microsomes and primary

hepatocytes of mouse, rat, dog, monkey and human. The *in vivo* metabolism of elafibranor was also studied in mice, rats and cynomolgus monkeys.

2.5.3.1. Methods of analysis

Suitable and validated methods for the detection of plasma concentration of elafibranor were provided. Bioanalytical methods have also been developed and validated for the measurement of the active metabolite GFT1007 (all species) and the inactive metabolites GFT3351 (all isomers) and GFT4775 (all isomers) (rat and monkey plasma). All methods rely on liquid chromatography with tandem mass spectrometry (LC-MS/MS) for analyte detection, by using reversed phase high performance liquid chromatography (HPLC) with electrospray ionisation MS/MS detection. The detection range for elafibranor was 1-1000 ng/ml in mouse plasma, 0.5-500 ng/ml in rabbit plasma and 5-5000 ng/ml in rat, dog and monkey plasma. The detection range for GFT1007 was 5-5000 ng/ml in rabbit plasma, 10-5000 ng/ml in mouse plasma, 50-20000 ng/ml in dog plasma, 50-50000 ng/ml in rat plasma and 0.1-100 µg/ml in monkey plasma. The detection range for GFT4775 in rat and monkey plasma was 3.0901-1595.0 nM and the detection range for GFT3351 in rat and monkey plasma was 2.1528-1076.4 nM. Tissue distribution of radioactivity in mice and rats was analysed using quantitative whole-body autoradiography or by liquid scintillation counting.

2.5.3.2. Absorption

The plasma PK of elafibranor was investigated after single IV or oral administration of 14C labelled elafibranor in rats, dogs, monkeys and minipigs. Elafibranor was rapidly absorbed in all animals (Tmax 0.5-2 h), as well as in humans (Tmax 1.25h). After oral administration, bioavailability was moderate in dogs and monkeys (both 41%) and rats (62%) and high in monkeys (81%). Bioavailability in human has not been determined. Elimination half-life of elafibranor after oral administration was 2-2.4h in rats, 6.8h in dogs, 9.2h in minipig and 6.6-29.2h in monkeys.

PK parameters of the active major metabolite GFT1007 were also determined in rat and monkey. After oral administration, Tmax was 1-2.7h. Elimination half-life of GFT1007 was 2.2 h in rat and 13.3-17.5h in monkey. The AUC of GFT1007 represented 1407% of the exposure of elafibranor in rats and 2260% of the exposure of elafibranor in monkeys, indicating significant exposure for both metabolites.

Plasma clearance and volume of distribution of elafibranor in rat were 0.55 L/h and 1.66 L. Clearance and distribution volume of individual metabolites were not evaluated. However, clearance and distribution volume based on total radioactivity in plasma of rats, dogs, monkeys and minipigs was calculated in a preliminary PK and excretion study. The results showed low clearance in all animal species tested, low volume of distribution in dogs and moderate volume of distribution in rats, monkeys and minipigs.

In the single dose PK studies in rat and monkey, exposure for GFT3351 and GFT4775 was provided. AUC levels represented 9.7% and 370.8% of the exposure of elafibranor in rats and 1600% and 600% of the exposure of elafibranor in monkeys, indicating that also these metabolites are major metabolites in rats and monkeys, as they are in humans.

The pharmacokinetics following repeated dosing of oral elafibranor was investigated in rats, dogs and monkeys. Overall, a dose-linear relationship for exposure of elafibranor and GFT1007 was observed. In general, no gender differences were observed for elafibranor, although in rats, exposure in males was slightly higher than in females. For GFT1007, exposure in female rats was slightly higher than in male rats. No minimal accumulation was observed for elafibranor (mean over studies 1.8-2.5x in rats and 1.5-2.7x in monkeys) or GFT1007 (mean over studies 0.4-0.9x in rats and 1.1-3.3x in monkeys). No difference in exposure was observed between pregnant and non-pregnant animals following repeated administration of elafibranor to rats and rabbits.

2.5.3.3. Distribution

Plasma protein binding of elafibranor and the major active metabolite GFT1007 was studied using equilibrium dialysis. In humans, over 99% of elafibranor and GFT1007 was bound to plasma proteins and binding was not concentration dependent. The majority of binding was to human serum albumin. Also, in animal species protein binding was high (>97%). Fraction unbound of elafibranor was 0.024 in mice, 0.018 in rat, 0.014 in dog, 0.016 in monkeys and 0.006 in humans. Fraction unbound of GFT1007 was 0.092 in mice, 0.015 in rat, 0.016 in dog, 0.022 in monkeys and 0.004 in humans. Plasma protein binding of the inactive major metabolite GFT3551 was also analysed in humans, but not in animals. Considering the moderate plasma protein binding of this racemic metabolite (76-80%), this is acceptable. However, plasma protein binding of the inactive metabolite GFT4775 was not analysed.

The distribution of elafibranor has been studied using quantitative whole-body autoradiography (QWBA) after single oral administration of 14C-labelled elafibranor (10 mg/kg in male CD-1 mice, 10 mg/kg in male Sprague-Dawley rats, or 50 mg/kg in male and female Cynomolgus monkeys). Radioactivity from 14C-elafibranor was rapidly and widely distributed throughout all three species. In general, similar distribution profiles were observed in mice, rat and monkey. Radioactivity concentrations in blood cells were lower than in plasma, indicating no red blood cell binding. Tissue: plasma ratios were <1 in most tissues. Highest concentrations were observed in tissues associated with excretion (including the gastrointestinal tract, kidney, and urinary bladder wall), liver, and bile. Radioactivity was still detectable in several tissues at 24h (last point of analysis for monkey), but at 168 hours post-dose, concentrations in all tissues were below the limit of quantification in mice and rat.

Since only albino mice and rats were used, melanin binding could not be analysed. Gender differences were not investigated in mice and rats since only male animals were used. However, in monkey, distribution was similar between males and females.

Neither placental transfer studies, nor excretion studies in milk have been performed with elafibranor. However, in the rat PPND study, GFT1007 has been detected in 2 pups at LD14, suggesting that there may be some transfer from elafibranor and/or GFT1007 via placenta and/or milk. SmPC 4.6 advises that elafibranor should not be used during breastfeeding and for at least 3 weeks following last dose of elafibranor.

2.5.3.4. Metabolism

Studies with ^{14}C-elafibranor in liver microsomes (from rat, dog, monkey and human) using a radioactivity-coupled chromatographic method showed that elafibranor was more rapidly metabolised by rat and monkey microsomes than by dog and human liver microsomes. The most predominant metabolite in all species was GFT1020 (resulting from the S-oxidation of elafibranor). GFT1326 (resulting from the reduction of the carbonyl moiety of elafibranor) was also detected at significant levels in dogs, but at lesser amounts in the other species. GFT1007 was also observed in all species and was more rapidly metabolised by rat than human liver microsomes. GFT1007 was further metabolised into GFT1119 (resulting from reduction of the carbonyl moiety of GFT1007), GFT1686 (resulting from oxidation of the sulphur atom), 2 metabolites resulting from hydroxylation of GFT1007 and one metabolite resulting from either oxidation of GFT1119 or reduction of the carbonyl moiety of GFT1686. GFT1119 and GFT1686 were not observed in dog microsomes.

GFT1119 is a chiral compound, of which both enantiomers (GFT1590 and GFT15910) were detected in dog and human liver microsomes, whereas in rats and monkey microsomes only the enantiomer GFT1590 or GFT1591, respectively was generated.

Phase II reactions included glucuronidation reactions and glutathione conjugations.

A GLP-compliant study with ^{14}C-elafibranor and ^{14}C-GFT1007 in mouse, rat, dog, monkey and human primary hepatocytes found 28 different metabolites, indicating a rapid and extensive metabolism.

A study with human intestinal microsomes resulted in the detection of five phase I metabolites, including GFT1007, GFT1020, and GFT1326.

In vivo metabolism of elafibranor was studied in rat and monkey plasma. At 0.5-1 h, GFT1007 was the major metabolite found in rat and monkey, whereas at 12-24 h predominantly GFT1119 and oxides thereof were found. In humans, GFT1119 was only observed in faeces at a very low amount (0.94% of dose) and is thus not a major metabolite. In monkeys, also an isomer of GFT1686 was detected.

The single dose pk studies in rat and monkey, indicated that the total exposure of GFT1007, GFT3351 and GFT4775 represented 1407%, 9.7% and 370.8% of the exposure of elafibranor in rats and 2260%, 1600% and 600% of the exposure of elafibranor in monkeys. In humans, these metabolites represented 46, 29% and 13% of the administered dose and should therefore all three be considered as major metabolite.

In urine of both species, oxides of GFT1119 were prominent components. Parent compound and GFT1007 were not or almost not excreted in urine. GFT1686 was also found in female rat urine, but much less in male rat urine. Monkey urine also contained GFT3351. In rat bile, a sulfate conjugate of GFT1007 was detected, whereas in monkey bile the glucuronide conjugates GFT3282, GFT3351 and GFT1119 glucuronide were more abundant. In feces, unchanged elafibranor was the major component. GFT1007 was more significant in monkey faeces, while GFT1119 and the oxidised metabolites thereof were present in both species.

2.5.3.5. Excretion

Excretion was studied in GLP-compliant studies after single oral and IV administration in the rat and the monkey. Results from a pilot study are available for dog and minipig. Elafibranor and its metabolites are rapidly cleared from the plasma in all species. After 168 hours, total recovery of radioactivity was 95-102%, and 76-92%, respectively, in rat and monkey. In rat, elafibranor-related material was predominantly excreted via the fecal route, irrespective of the administration route, although in females, urinary excretion was higher than in males (fecal excretion 83-90% and 69-71% in males and females, respectively; urinary excretion 12% and 27-30% in males and females, respectively). In bile-duct cannulated rats, 71% of radioactivity was recovered in bile in the first 24 h, indicating biliary excretion is a major pathway. In the same study it was found that the biliary excretion was associated with a significant enterohepatic cycle.

In monkeys, fecal excretion was predominant after oral administration (40-46%), with 22-27% of the radioactive material excreted via urine, whereas after IV administration, urinary excretion tended to be slightly higher than fecal excretion (29-38% urinary excretion vs 21% fecal excretion). No differences between males and females were observed.

Also in humans, excretion is mainly via the fecal route (77.1% of a 120 mg oral dose, primarily as elafibranor [56.7%] and GFT1007 [6.08%]), with urine contributing for 19.3% (primarily as glucuronide conjugates).

2.5.3.6. Pharmacokinetics drug interactions

These are discussed in the clinical PK sections.

2.5.3.7. Other pharmacokinetic studies

Elafibranor was investigated in rodent models of NASH (mice) and Hepatic Fibrosis (rats), to investigate the concentrations of elafibranor and GFT1007 in plasma, liver and bile samples after single or repeated (30 mg/kg/day for 7 weeks) administration of elafibranor. In both models, GFT1007 was

detected at higher concentrations in plasma and liver than elafibranor. No accumulation of either elafibranor or GFT1007 was observed. In bile, elafibranor and GFT1007 were detected at similar levels in the NASH mouse model, and elafibranor was detected at higher levels that GFT1007 in the rat fibrosis model.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Although the performance of single dose toxicity studies is not recommended by ICH M3 guideline, four single dose toxicity studies (conducted in 2005) have been submitted by the applicant. Acute toxicity of elafibranor was studied by oral and IV route in rats and mice. The oral and IV LD50 values were > 2000 mg/kg and > 300 mg/kg, respectively. Administration of elafibranor caused no treatment-related clinical signs or changes in body weight, with the exception of slight tendency to hypothermia in the IV study in rats, which is likely not clinically relevant.

2.5.4.2. Repeat dose toxicity

Pivotal repeated dose toxicity studies were conducted in rats (28-day, 13- and 26-week), monkeys (28-day, 13- and 52 weeks), dogs (28-day) and mice (13-weeks).

The 28-day study in dogs was conducted under GLP; however, it was declared non-GLP-compliant due to the presence of the test substance in the TK samples from 2 animals of the control group. Therefore, it has been included in the table with non-pivotal studies in this section; however, as its results are considered to be highly relevant to the toxicological profile of elafibranor, it is also discussed below.

Rats

In all studies, adverse effects on the liver and selected haematological parameters were seen already from the lowest tested dose levels (30, 3 and 3 mg/kg/day, respectively). Generally, at the lowest dose levels the increases in liver weights and hepatocellular hypertrophy were observed; additionally, hepatic coagulative focal necrosis was observed in some animals in the 28-day and 26-week study, and (minimal) bile duct proliferation was seen in 2 low-dose animals in the 26-week study. At higher dose levels, the effects additionally included more pronounced bile duct proliferation, increased ALP levels and decreased fibrinogen. Markers of liver injury ALAT and ASAT were increased only in the 28-day study starting from the mid-dose.

While fibrates are known to be lipid-lowering drugs leading to decreased triglyceride and cholesterol levels, elafibranor treatment generally led to an increase in total and LDL cholesterol at the top dose levels across all studies, without appreciable effect on triglycerides. Decreased triglyceride levels were seen only in high-dose females of the 28-day study and in all treated females in the 26-week study.

Possibly secondary to the liver effects were the increased thyroid weights at all dose levels in females and the observation of thyroid follicular epithelial hyperplasia in most high-dose animals in the 28-day study. Effects on thyroid are often observed in rodents secondary to the liver enzymes activation, leading to the reduction of circulating thyroid hormones, increased TSH levels and subsequent thyroid gland stimulation. Such effects are, however, considered to be a low relevance to humans, as lower circulating levels of thyroid hormones due to liver enzyme inducers do not result in appreciable TSH increases in humans. Furthermore, no thyroid effects were observed in the 13- and 26-week studies.

Mild decreases in red blood cell (RBC) count and haemoglobin were generally seen starting from the lowest dose levels across the studies. However, reticulocytes were not increased, and there was no sign of compensatory haematopoiesis in the bone marrow; only in the 26-week study extramodular splenic haematopoiesis was seen in high-dose males. At higher dose levels, platelet levels were increased (particularly in males) and prothrombin times were decreased in both sexes. Increased heart weight and focal myocarditis was observed at 100 mg/kg/day in 28-day and 26-week studies. In the 26-week study, however, focal myocarditis was also observed following the recovery period in 4/6 control males, therefore the finding in the treated high-dose males was considered to be not related to treatment by the study director. Considering similar observations at the same dose level in the 28-day the relevance to treatment cannot be excluded; however, there was no effect on the marker of cardiac injury, troponin I, in either 13- or 26-week study.

Generally, effects on the liver were largely, but not completely reversible upon recovery, with increased liver weights and/or bile duct proliferation still observed in high-dose recovery animals. No haematological effects were usually seen after the recovery period.

Increased homocysteine levels were observed from the mid-dose levels in the 26-week study. No effect on adiponectin levels, the marker of PPARγ activation, was observed in the 26-week study.

Increased kidney weights without histopathological correlate were observed at all dose levels in the female rats in the 28-day study. In the 26-week study, increased kidney weights were seen in males starting from 30 mg/kg/day; histopathologically they were correlated with focal tubular basophilia.

Based on the liver and haematological effects at all dose levels, the lowest tested dose levels of 30, 3 and 3 mg/kg/day(at 4, 13, 26 week studies, respectively).

were considered to be LOAELs in all studies. It is noted that the applicant has considered the effects on liver and haematological parameters observed at the lowest tested dose levels to be non-adverse based on their small magnitude and the fact that rats are known to be more sensitive to PPAR activation than humans. However, as the observed effects showed a clear dose-response, a statistical significance was generally reached for haematological effects at least in one sex, there was an effect on hepatic clinical chemistry parameters (ALP increase), and the histopathological effects which were considered adverse at higher dose levels (e.g. bile duct hyperplasia), were already also seen at the lowest dose levels, albeit of lower severity and incidence, the CHMP considered it more appropriate to regard the lowest tested dose levels as LOAELs. The calculated exposure margins at the LOAELs relative to clinical exposure based on the $AUC_{0\text{-}t}$ were generally very low for both elafibranor and its metabolite GFT1007. In particular, in the study of the longest duration (26-week), they were 0.2 and 0.02 for males and females for elafibranor and 1.2 and 5.8 for GFT1007. It is however noted that rats are more sensitive to PPAR activation than humans.

Toxicokinetic analysis at Week 13 and Week 26 revealed that plasma exposure of elafibranor and its major circulating metabolite GFT1007 increased with administered dose. However, a difference was found between the C_{max} and AUC values of elafibranor and GFT1007 in males and females (i.e., higher exposure of elafibranor in males and higher exposure of GFT1007 in females), suggesting a potential sex-related metabolic difference.

The applicant acknowledges that exposure to elafibranor and/or GFT1007 was slightly different between males and females after repeated dosing in the rat toxicity studies. However, no sex differences in metabolism were observed in the other species. Furthermore, in a population PK analysis involving 894 patients with PBC, no clinically relevant sex differences were observed in the AUCт, Cmax or Cmin of elafibranor or GFT1007. This lack of sex-related PK variability was evident in both healthy subjects and patients with PBC. In conclusion, based on these data, gender is unlikely to have a significant impact on the safety or efficacy of elafibranor in the treatment of PBC.

Monkeys

The effects in monkeys were overall similar to the effects in rats, but less pronounced. Increased liver weights accompanied by hepatocellular hypertrophy and multifocal single cell degeneration/ necrosis/ apoptosis of hepatocytes were generally observed in individual mid-dose animals and most high-dose animals in the 13- and 52-week studies. There were no effects on the liver enzymes which are considered to be markers of hepatic injury (ALAT, ASAT). The observed effects were mostly recoverable, with only inflammatory cell foci seen with a slightly higher incidence in the high-dose animals of the 52-week study at the end of the recovery period. ALP levels were generally decreased across the studies at the top dose levels, in contrast to rats, where ALP increases were observed. Decreased bilirubin levels were observed in the 28-day and 52-week study at the top dose levels.

Similarly to rats, moderate increases in total and LDL cholesterol were observed across the studies (high dose males in the 4-week study and in both sexes in the 52-week study (52-week study: total: +61% in males, + 50% in females, LDL: +79% in males, +69% in females at the top dose). There was no effect on triglyceride levels.

Sightly reduced levels of RBC-related parameters (RBC count, Hb, PCV, MCV) were observed in the high-dose animals of the 28-day and 13-week studies, and at interim evaluations (12 and 25 weeks) in the 52-week study; however, at the end of the exposure period in the 52-week study there were no effects on haematological parameters. Decreased cellularity of bone marrow caused by higher amount of adipose tissue was observed in high-dose animals of the 13- and 52-week studies and mid-dose males of the 52-week study, but this effect was no longer observed after the recovery period. In the 13-week study, the bone marrow differential cell count showed a lower quantity of PCE, normoblasts and total erythroid series, indicating non-regenerative anaemia. The effects on RBC-related parameters in the 13-week study were not fully reversible, with individual values of Hb and PCV in high dose mails still slightly lower than in controls. However, it needs to be noted that these effects were not seen at the same dose level in the 52-week study.

Some ECG changes (biphasic T-waves in males and reduced T-wave amplitude in females) were seen at the high-dose of 100 mg/kg/day in the 28-day study; however, these changes were not observed at the high-dose levels of 50 mg/kg/day in the 13- and 52-week studies, with comparable exposure levels (C_{max}) reached in the 52-week study. There was also no effect on the cardiac injury marker troponin I in any of the studies.

Reduced thymus weight and thymus degeneration/atprophy were seen at 100 mg/kg/day in the 28-day study; however, no effect was observed in the high-dose animals (50 mg/kg/day) in the 13- and 52-week studies.

Foci of degeneration/regeneration in diaphragm muscle were seen in high-dose animals of both sexes in the 52-week study; the effect was reversible following the recovery period.

Lower weight of reproductive organs (testes and epididymides in males, ovaries in females) and less mature testes, ovaries and utera were seen in the high-dose animals in the 52-week studies. However, as animals did not reach sexual maturation during treatment, these effects may be secondary to reduced body weights and not directly related to the pharmacological action of the substance.

Increased homocysteine levels were consistently seen in the treated animals across all three studies; in the 13-week study the increase was seen already at the low dose in males and at the mid-dose in females.

In the study of the longest duration (52 weeks), the NOAEL was considered to correspond to 10 mg/kg/day, corresponding to exposure multiples of 0.5 and 0.4 for elafibranor and 4.3 and 3.6 for GFT1007 for males and females, respectively. It is noted that the applicant considered the highest

tested dose level of 50 mg/kg/day to be NOAEL, as the effects observed at this level were regarded as non-adverse; however, taking into account the complete scale of effects seen at the high dose level (body weight loss, histopathological changes in liver with hepatocellular degeneration/necrosis and inflammatory foci, which were not fully reversible, foci of degeneration in diaphragma muscles, adipose tissue in bone marrow) the NOAEL is set at 10 mg/kg/day by the CHMP.

Dogs

The effects in dogs were overall similar to rats and monkeys; however, much more significant effect on haematological parameters was observed. In the 28-day study with dogs, reduced levels of RBC and haematocrit were observed already from the lowest dose level of 3 mg/kg/day (-10.9% and -13.9%, respectively). These effects became significantly more pronounced at higher dose levels, with ca. -45% decrease in RBC, Hb and HCT at the top dose level of 300 mg/kg/day. From 30 mg/kg/day, also decreased levels of WBC, neutrophils and eosinophils were seen, reaching respectively -34%, -45% and -80% decrease at the top dose level of 300 mg/kg/day.

Increased liver weights were observed from 100 mg/kg/day, which correlated hystopathologically with periacinar hepatocytic hypertrophy at 300 mg/kg/day. At the top dose level ASAT was increased; however, the magnitude of the increase (56%) is considered too low to signify the liver injury. Total cholesterol was decreased starting from 30 mg/kg/day; no effect was seen on triglyceride levels. Glucose, albumin and creatinine levels were decreased at the top dose of 300 mg/kg/day. Notably, there was no effect on the ALP levels.

Thymic atrophy was observed in female dogs starting from 30 mg/kg/day and in male dogs from 100 mg/kg/day. Cardiac steatosis, auricular and ventricular, was seen in 2 females at 300 mg/kg/day and auricular steatosis was seen in 2 females of 30 and 100 mg/kg/day groups. Although the study director considered these lesions to be unrelated to treatment and to represent a usual finding in dogs, these effects were not seen in controls, and the marker of cardiac injury, troponin I, was also increased at 300 mg/kg/day, indicating possible treatment-related effect. However, there were no ECG changes at any dose levels.

Based on the effects on red blood cells from the lowest dose level, the lowest dose level of 3 mg/kg/day is considered to be a LOAEL. No exposure multiples could be calculated at this dose level for elafibranor because of the lack of reliable AUC values. For GFT1007, they were 0.6 and 0.8, respectively.

Mice

Adverse effects on the liver, manifested as increased weights correlated with hepatocellular hypertrophy, eosinophilia and vacuolation, decreased glycogen content and increased ALP levels, were seen starting from the lowest dose level of 3 mg/kg/day. Starting from 10 mg/kg/day, single cell necrosis, hepatocellular polyploidy and increase in mitotic figures in the liver was also observed. No evaluation of haematological parameters was performed. Based on the liver effects, the lowest tested dose level of 3 mg/kg/day is considered to be a LOAEL.

2.5.4.3. Genotoxicity

Genotoxicity of elafibranor was studied in the GLP-compliant Ames test and *in vitro* mouse lymphoma assay. Additionally, the applicant has submitted non-GLP compliant screening Ames test (TA98 and TA100 strains only), *in vitro* micronucleus test in mouse lymphoma cells and the 2nd *in vitro* micronucleus test in mouse lymphoma cells with and without exposure to natural light. As stated in the study report, the latter study was apparently conducted as the test substance elafibranor (trans-isomer) can isomerise into pharmacologically inactive cys-form under the presence of natural light.

Elafibranor did not increased the number of revertants in the Ames test (*S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537) both in the presence and absence of metabolic activation, when tested up to cytotoxic concentrations. The substance, however, produced positive response in the gene mutations study at the TK locus in mouse lymphoma L5178Y cells in both replicate assays (1st assay: positive -S9, equivocal + S9; 2nd assay: positive ± S9), with an increase in the number of total and small colonies, when tested up to cytotoxic concentrations. The increase in the number of small colonies is consistent with clastogenic response. The latter results were further supported by the positive outcomes of two non-GLP-compliant micronucleus assays in mouse lymphoma cells. The first one, conducted both with and without metabolic activation, showed positive response at 4 hr treatment followed by 24 hr recovery period. The 2nd one, conducted with and without exposure to natural light only in the presence of metabolic activation, also showed positive response under the same test conditions. Altogether, the results suggests that elafibranor exhibits clastogenic activity *in vitro.*

However, elafibranor produced negative results in two *in vivo* oral micronucleus tests in rats when tested up to the limit dose of 2000 mg/kg (2 administrations 24 hr apart). Bone marrow was sampled 24 hr after the last administration. There was no effect on PCE/NCE ratio; however, systemic exposure to the test substance was adequately demonstrated in peripheral blood 1 or 2 hr post-administration. In the 2nd study, also plasma concentrations of the metabolite GFT1007 were determined. As bone marrow is a highly perfused tissue, it can be concluded that adequate exposure to both the parent substance and its major pharmacologically active metabolite was achieved.

Additionally, elafibranor produced negative results in the GLP-compliant *in vivo* UDS test and Comet test in rat liver, when tested up to the limit concentration of 2000 mg/kg/day. Together the submitted information is considered to provide an adequate proof that elafibranor is not genotoxic *in vivo*.

Metabolite GFT1007:

Genotoxicity of the pharmacologically active metabolite GFT1007 was evaluated in a GLP-compliant Ames test (*S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537), and a non-GLP-compliant *in vitro* micronucleus test in mouse lymphoma L5178Y cells. Both tests produced negative results, when tested up to cytotoxic concentrations, both with and without metabolic activation. Additionally, exposure to GFT1007 was demonstrated in one of the two *in vivo* micronucleus tests conducted with elafibranor (test report GFT505-tox4-003d). Taken together, the overall evidence is considered sufficient to conclude on the lack of genotoxic potential of GFT1007.

Metabolite GFT3351:

Genotoxicity of metabolite GFT3351 was assessed in two GLP-compliant *in vitro* tests, namely an Ames test (*S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537) and an *in vitro* micronucleus test in human lymphocytes. Both tests were conducted up to the top concentration of 20000 µg/plate and 2000 µg/mL, respectively, with the aim to achieve the limit concentration of 5000 µg/plate or 500 µg/mL for each of the four enantiomers in the racemic mixture, as recommended by the current ICH S2(R1) guideline. There was no cytotoxicity, but precipitation was observed at the highest tested concentration in the presence of S9 mix in the Ames test. The test substance produced negative results in both tests both with and without metabolic activation.

2.5.4.4. Carcinogenicity

Carcinogenicity of elafibranor was tested in rats and mice. In the GLP-compliant 104-week study with Sprague-Dawley rats, elafibranor induced increased incidence of hepatocellular carcinomas/adenomas and pancreatic acinar cell adenomas in both sexes and pancreatic cell adenomas in females. The NOAEL for neoplastic lesions was 3 mg/kg/day in males and 10 mg/kg/day in females. In addition,

increased incidence of preputial gland carcinomas was seen in the high-dose males (4 vs 0 in concurrent controls, 6.7%) which was outside the historical control range of the testing laboratory (0.24-1.43%) and literature data (0.77-1.85%). Statistically significant positive trend was also observed for preputial gland carcinomas and papillomas combined (p = 0.0054). However, since the incidence of squamous cell carcinoma was not statistically significantly different from concurrent controls (p = 0.0534), the relationship with elafibranor treatment was considered to be equivocal by the study director.

In the GLP-compliant carcinogenicity study with Swiss mice, elafibranor induced increased incidence of hepatocellular carcinoma, adenoma and adenoblastoma at all dose levels. No other (pre)neoplastic lesions were observed in other organs and tissues.

2.5.4.5. Reproductive and developmental toxicity

In the GLP-compliant fertility and early embryo-foetal development study with SD rats, there appeared to be a minor effect on male fertility at the highest tested dose of 100 mg/kg/day. This included a slight decrease in mean daily testicular sperm production, an increase in the mean number of epididymal spermatozoa, a slight decrease in the epididymal sperm motility and a minor decrease in the percentage of sperm cells with normal morphology. However, the first three parameters still remained within the historical control data of the testing laboratory and thus were considered to have no toxicological relevance by the study director. The decrease in the percentage of sperm cells with normal morphology was a result of an increased percentage of epididymal sperm morphology defect (normally shaped head separated from the flagellum and degenerative flagellar defect with normal head) which was outside the historical control range and was thus considered related to treatment. Possibly secondary to these effects were the reduced female fertility index (85% vs 91.4% in controls), reduced number of live concepti (88.5% vs 91.4% in controls) and a higher number of post-implantation loss (11.5% vs 8.6% in controls) at the same dose level. There also appeared to be a minor effect on oestrous cycle in females, with increased number of days of diestrus (6.5 vs 5.6 days in controls) and estrus (4.0 vs 3.5 days in controls) and decreased number of days of metestrus (1.9 vs 3.1 days in controls). However, there were no statistically significant effects of test item treatment on mean cycle length or the percentage of females with normal cycles.

The toxicokinetic analysis was not performed; however, the top dose level was identical to the top dose level tested in the 26-week repeated dose study with rats, which allows for a rough estimate of exposure levels.

To follow up the findings of this study, the second FEED study was conducted in which only males were treated with elafibranor for a total of 9 weeks (at least 4 weeks before mating) up to the same dose of 100 mg/kg/day and then paired with untreated females. There was no effect of elafibranor administration on the mean total sperm count, the percentage motile, velocity or path straightness. There was no effect on sperm morphology; values were similar to the controls. At female necropsy, there was no effect of male administration with elafibranor on pregnancy parameters, characterised by the mean number of implantations, mean percentage pre- and post-implantation loss, or the mean number of live foetuses. There were 3 females in the high-dose group with high post-implantation loss; however, there was no clear correlation with male sperm parameters. Out of these three females, only one was mated with a male with a low number of normal sperm; however, a comparable sperm count was seen in one of the control males as well. Other two females were mated with males with normal sperm parameters. Therefore, in the absence of an effect on mean data, the findings are considered to be of no toxicological significance. Sufficient exposure multiples were achieved in the study at the NOAEL (26.8 for elafibranor and 36.6 for GFT1007 based on AUC_{0-24}).

Embryo-foetal toxicity of elafibranor was evaluated in two GLP-compliant studies with rats and rabbits. In rats, adverse effects on embryo-foetal development (increased post-implantation loss, decreased number of live foetuses and decreased mean foetal body weight) were observed only at a very high dose level of 1000 mg/kg/day causing significant maternal toxicity (poor clinical condition, body weight loss, significantly increased liver enzymes). There were no malformations, but there was an increased number of foetuses with shortened innominate artery and incomplete ossification. The NOAEL for developmental toxicity was considered to be 300 mg/kg/day, while the NOAEL for maternal toxicity was 30 mg/kg/day based on liver effects.

In the study with rabbits, increased incidence of foetal malformations, primarily concerning heart and/or great vessels malformations, was seen at the top dose of 300 mg/kg/day. These included cardiomegaly, atrial septum defects, ventricular wall defects and malpositioned or absent arteries. There was also an increased number of foetuses with absent innominate artery, which may be correlated with a shortened innominate artery observed in the top dose foetuses in the rat EFD study. There were also two foetuses missing kidney and ureter. Additionally, there was an increased incidence of foetuses with structural malformations and variations, in particular malrotated paws or short tails, fused, misaligned or lower number of caudal vertabrae; misschapen or bent humerus, femur and tibia. There was also an increased post-implantation loss, decreased number of foetuses and live foetuses and reduced foetal body weight. These effects occurred in the presence of maternal toxicity (reduced body weight and body weight gain, increased liver weights and significantly increased cholesterol (+475%), triglycerides (+52%) and creatinine (+21%) levels). At the mid-dose of 100 mg/kg/day adverse foetal effects were limited to incomplete ossification of fore- and hindpaws, the pubis, metacarpal and talus which were considered related to treatment. Maternal toxicity was evidenced only as a slightly lower body weight and body weight gain. Finally, at the lowest dose level of 30 mg/kg there were 1 foetus with malpositioned pinna, amelia, thoracoschisis and meningocele and 1 foetus with an omphalocele. Furthermore, one foetus with omphalocele was also observed in the preliminary DRF rabbit study, which may suggest that this effect was treatment related. However, omphalocele was also reported as a common non-specific malformation in NZW rabbits (Daston, 2018). Meningocele was also observed in one foetus of the control group which suggests that this may have been an incidental finding. Taking into account that neither meningocele nor omphalocele were observed at higher dose levels, the literature data suggesting that omphalocele is a common malformation in NZW rabbits and occurrence of meningocele in one of the control animals, it is considered unlikely that these findings were related to elafibranor treatment. The NOAEL for developmental toxicity in rabbits is considered to be the lowest dose level of 30 mg/kg/day. This corresponds to very low exposure multiples (0.001 for elafibranor and 0.4 for GFT1007 based on the $AUC_{0\text{-}24}$), suggesting possible clinical relevance of the observed effects.

In the GLP-compliant pre- and post-natal development study with rats, reduced pup survival, reduced body weight and delay in pinna unfolding was observed already at the lowest tested dose of 10 mg/kg/day. Other delays in developmental landmarks were seen at higher dose levels (eye opening, air righting reflex). Elafibranor-related clinical observations (including blue coloration and blackened, dead tissue; cold to the touch; thin fur; small size; and weak and impaired mobility) were evident in pups at all tested dose levels. Macroscopically, these observations correlated with a dose-related increase in dilated and/or pale abdominal blood vessels in F1 pups from all elafibranor-treated dams which were found dead or sacrificed. Microscopic examination revealed dose-related increase in vascular thrombi in the abdominal and/or iliac arteries of F1 pups following maternal exposure to 30 or 100 mg/kg/day. These effects occurred in absence of appreciable maternal toxicity. Maternal toxicity was manifested only as lower body weights during LD1-7 and lower food consumption during lactation in dams administered 100 mg/kg/day. Three females administered 30 mg/kg/day and four females administered 100 mg/kg/day were removed from the study due to total postnatal litter losses. The total litter losses were considered substance-related at 30 and 100 mg/kg/day based on the dose

responsive increase in incidence over concurrent control values, and the fact that the incidences were greater than observed in historical control data (0-2). Gestation length appeared to be shortened for all test article-treated groups, compared with controls. Relevant findings from this study are described in 5.3 of the SmPC.

In the F1 generation, the attainment of sexual maturation was marginally delayed for both sexes maternally exposed to 100 mg/kg/day, and for females maternally exposed to 30 mg/kg/day, compared with controls. Caesarean data from F1 females indicated marginally higher pre-implantation loss in the group maternally exposed to 100 mg/kg/day, compared with controls. Other pregnancy parameters were unaffected.

Based on the results of the study, the lowest tested dose level of 10 mg/kg/day was considered to be the LOAEL for F1 generation development, corresponding to EM of 0.3 for elafibranor and 7.1 for GFT1007 at the LOAEL level based on $AUC_{0\text{-}24.}$ The dose level of 30 mg/kg/day was considered the NOAEL for maternal toxicity based on reduced body weight and food consumption at the next dose level.

Elafibranor was not measurable in plasma samples from F1 generation pups, while its metabolite GFT1007 was measurable in only two samples from F1 generation pups from litters of dams administered 100 mg/kg/day. While milk samples were taken from the dams, they were not further analysed, as the pup plasma levels were negligible.

In the GLP-compliant study with juvenile rats exposed from PND21 to PND61, adverse effects on the liver and the RBC-related parameters were seen in both sexes already at the lowest tested dose level of 10 mg/kg/day. These effects were similar to the adverse effects in adult animals in the repeated dose toxicity studies. Increased liver weights which correlated with diffuse hepatocellular hypertrophy and increased ALP levels were observed in both sexes, and increased ALAT levels were observed in males from 10 mg/kg/day. Increased liver weights and ALP levels were still present in both sexes following the recovery period. Thyroid follicular cell hypertrophy was observed in the high-dose animals which was likely secondary to the induction of liver enzymes leading to the reduced thyroid hormone levels in circulation and thyroid gland stimulation.

The effects on RBC-related parameters were more prominent in males and encompassed small statistically significant dose-dependent decreases in HB, RBC and PCV together with decreased MCH and HDW and small increases in RET compared to the concurrent controls. Reduced RBC, Hb and PCV were still present after the recovery in males, although the values increased compared to the end of treatment. Additionally, dose-dependent increase in platelets was seen in males from 30 mg/kg/day.

Large kidneys were recorded in occasional males at all dose levels, and decreased urinary volume and increased specific gravity was seen in males from 30 mg/kg/day. Histologically, renal papillary mineralization was seen in males administered 100 mg/kg/day.

Also increased incidence of foamy histiocytes in the thymus and increased incidence of degranulation in pancreas were observed in the high-dose males.

Tibia length was 4% shorter compared to controls in animals administered 100 mg/kg/day which was still present after the recovery period.

There were no adverse effects on fertility and reproductive parameters (number of corpora lutea, implantation sites) in elafibranor-treated animals.

In summary, the effects of elafibranor on juvenile animals were comparable with the effects in adult animals, with main effects on liver and RBC-related parameters which were seen already from the lowest tested dose of 10 mg/kg/day. The long bone length was slightly reduced at 100 mg/kg/day.

Juvenile males appeared to be more sensitive compared to females, in particular with regard to the effects on RBC-related parameters and kidney toxicity.

Exposure to elafibranor did not adversely affect fertility and reproduction. Based on the effects on liver and RBC, the lowest tested dose level of 10 mg/kg/day is considered to be a LOAEL in this study, corresponding to exposure multiples of 0.8 and 0.1 for elafibranor and 12.5 and 15.0 for GFT1007 for males and females, respectively. It is noted however that PBC is not diagnosed in childhood, thus it is not expected that children will be treated with elafibranor.

2.5.4.6. Toxicokinetic data

The toxicokinetics following repeated dosing of oral elafibranor was investigated in rats, dogs and monkeys. Overall, a dose-linear relationship for exposure of elafibranor and GFT1007 was observed. In general, no gender differences were observed for elafibranor, although in rats, exposure in males was slightly higher than in females. For GFT1007, exposure in female rats was slightly higher than in male rats. No to minimal accumulation was observed for elafibranor (mean over studies 1.8-2.5x in rats and 1.5-2.7x in monkeys) or GFT1007 (mean over studies 0.4-0.9x in rats and 1.1-3.3x in monkeys).

Elafibranor was rapidly absorbed in all animals (Tmax 0.5-2 h), as well as in humans (Tmax 1.25 h). After oral administration, bioavailability was moderate in dogs and monkeys (both 41%) and rats (62%) and high in monkeys (81%). Bioavailability in human has not been determined. Elimination half-life of elafibranor after oral administration was 2-2.4 h in rats, 6.8 h in dogs, 9.2 h in minipig and 6.6-29.2 h in monkeys. In humans, Population PK estimated the elimination half-life at 59.7 hours for elafibranor and 10.7 hours for GFT1007.

The applicant has provided exposure multiples based on the combination of elafibranor and GFT1007. This is not agreed, as there may be off-target effects that are specific for one of both compounds. Therefore, the CHMP has recalculated the exposure multiples, based on the individual exposure of either elafibranor or GFT1007. In addition, the CHMP has included exposure multiples based on Cmax values.

2.5.4.7. Local tolerance

No information on local tolerance has been provided. However, taking into account the intended route of administration (oral) and the lack of signs of irritation in the repeated dose toxicity studies the conductance of additional studies is not considered necessary.

2.5.4.8. Other toxicity studies

Elafibranor was found to be phototoxic *in vitro* in a GLP-compliant 3T3 NRU phototoxicity test with Balb/c 3T3 mouse fibroblasts. In the follow-up GLP-compliant *in vivo* UV-LLNA mouse study, positive result increased ear weight index (>1.05) was observed at the highest tested dose due to the findings in a single mouse (transient erythema, increased ear and lymph node weights). As the findings were observed in a single animal at high exposure multiples, elafibranor is not considered to raise a concern for phototoxicity in clinical settings.

The metabolite GFT1007 was not phototoxic *in vitro* in a GLP-compliant 3T3 NRU phototoxicity test with Balb/c 3T3 mouse fibroblasts.

2.5.5. Ecotoxicity/environmental risk assessment

Table 2: Summary of main study results

Substance (INN/Invented Name): elafibranor					
CAS-number: 923978-27-2 (single stereoisomer)					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} 3.90 (pH 5) log D_{ow} 2.22 (pH 7) log D_{ow} 1.08 (pH 9) log K_{ow} 5.15 (ion corrected)			not B
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	5.15			not B
Persistence	$DT50_{water}$ $DT50_{system}$ Values are derived from the OECD 308 study below and have been recalculated to 12°C	1.7 d, 1.7 d 1.7 d, 2.8 d			not P
Toxicity	NOEC	TBD*			TBD*
PBT-statement :	elafibranor is considered to be not PBT, nor vPvB				
Phase I					
Calculation	**Value**			**Unit**	**Conclusion**
$PEC_{sw\ refined}$ F_{pen} refined based on prevalence	0.016			µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption Soil 1 = silt loam Soil 2 = loam Soil 3 = sandy loam Sludge 1 = activated sludge Sludge 2 = activated sludge	OECD 106	$K_{oc,\ soil\ 1}$ = 1212 L/kg_{oc} $K_{oc,\ soil\ 2}$ = 1830 L/kg_{oc} $K_{oc,\ soil\ 3}$ = 1084 L/kg_{oc} $K_{oc,\ sludge\ 1}$ = 157.7 L/kg_{oc} $K_{oc,\ sludge\ 2}$ = 599.1 L/kg_{oc}			K_{oc} values in soil are based on Freundlich isotherms, K_{oc} values in sludge are based on K_d values.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = silt loam Sediment 2 = sandy clay loam	OECD 308	$DT_{50,\ water}$ = 0.8 / 0.8 d $DT_{50,\ whole\ system}$ = 1.3 / 0.8 d shifting to sediment = 47%, 25% CO_2 = 19%, 45% NER = 22%, 23% Transformation products >10% = Y GFT1020 = 32% GFT1007 = 35% GFT1686 = 38% metabolite 4 = 31% metabolite 2 = 11% DT50s for metabolites: GFT1007 = 13.2 / 24.5 d GFT1686 = 4.9 / 4.3 d			DT50s at 20°C 1 / 2 at day 14 at day 100 at day 100 DT50s at 20°C 1 / 2
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *R. subcapitata*	OECD 201	NOEC EC_{10}	≥0.096 >0.096	mg/L mg/L	growth rate growth rate

Daphnia magna, Reproduction Test	OECD 211	NOEC	≥0.026	mg/L	survival, reproduction, growth
Fish, Early Life Stage Toxicity Test/*P. promelas*	OECD 210	NOEC	≥0.072	mg/L	hatching, survival, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC_{10} NOEC EC_{10}	320 >1000 ≥1000 723	mg/L mg/L mg/L mg/L	total respiration total respiration nitrification nitrification
Phase IIb Studies					
Sediment dwelling organism/*C. riparius*	OECD 218	NOEC EC_{10} NOEC EC_{10}	≥5263 >5263 ≥5263 >5263	mg/kg_{oc} mg/kg_{oc} mg/kg_{oc} mg/kg_{oc}	emergence, emergence, develop. rate develop. rate

Conclusions on studies for elafibranor

Elafibranor is considered not to be PBT, nor vPvB. A risk to the STP, surface water, groundwater and sediment compartment is not anticipated based on the prescribed use of elafibranor.

2.5.6. Discussion on non-clinical aspects

Pharmacodynamics

The proposed mechanism of action is that elafibranor is a dual peroxisome proliferator-activated receptor (PPAR)α,δ agonist. The provided *in vitro* data could not fully substantiate elafibranor's role as a specific (PPAR)α,δ agonist. The *in vitro* PPAR nuclear reporter activation assay indicated that on human PPAR isoforms elafibranor was a pan PPAR agonist, with a notable likelihood of activating PPARγ. Additionally, elafibranor (and its metabolites) induced an increase in intracellular triglyceride content and adiponectin in human and murine adipocytes, indicating their *in vitro* PPARγ activity. Furthermore, toxicological effects associated with PPARγ activation (cardiomegaly, haemodilution and weight gain) were observed in *in vivo* primary PD and toxicological studies. While nonclinical findings could not rule out elafibranor's PPARγ agonism, the applicant provided evidence suggesting it is unlikely to cause PPARγ side effects due to its distinct hepatotropism and lack of distribution to fat tissue, where the PPARγ isoform is extensively expressed. The applicant reviewed literature on known PPARγ agonists and discussed the typical biochemical changes and adverse events associated with these agonists. The clinical data collected from Phase III studies of elafibranor (pivotal Study 319-1 and supportive Study 315-1) did not indicate PPARγ agonism, as shown by unchanged adiponectin biomarker levels and the absence of PPARγ activation effects, including changes in hematologic parameters, weight gain, fluid retention, edema, congestive heart failure, major adverse cardiovascular events, bone mineral density, and lipid parameters. In conclusion, the available data support that elafibranor is a PPARα and PPARδ agonist.

The submitted *in vitro* data validated the pharmacologically relevance of mice and rats for safety studies. Next to the papers of Guo 2007 and Waites 2007 cited previously, the applicant has provided references to the FDA reports on PPAR agonists (El-Hage 2005a and El-Hage 2005b). The reports indeed state that dogs are more sensitive to PPAR toxic effects than other species, and that it is recommended to conduct the general toxicity testing for this type of substances in rats and monkeys. Based on the provided evidence, dogs can be considered an appropriate species to be used in the cardiovascular safety pharmacology study (single dose) but not for the chronic safety assessment of elafibranor. The applicant acknowledges the lack of specific binding or gene expression data regarding monkeys' clinical relevance but highlights a high degree of homology between human and Cynomolgus

monkey PPAR isoforms. Together with the supporting pharmacokinetic data it can be agreed that monkey is a clinically relevant species.

Preventive effects of elafibranor and its main metabolite, GFT1007, on liver function and histologically assessed fibrosis, steatosis and inflammation was demonstrated in a well-recognized experimental model of NASH, developed in insulin-resistant mice. Besides, in a well-recognized liver fibrosis experimental model that elafibranor blocks the further development of established liver fibrosis and reverses CCl_4- induced macro- and microsteatosis as well as liver inflammation. Nevertheless, although elafibranor is effective in reducing steatosis in the NASH and CCL_4 animal models, it may not necessarily translate to a therapeutic benefit in PBC in human, as the underlying mechanisms and pathophysiology of PBC are distinct from those of steatosis-related liver diseases. Moreover, elafibranor administration was correlated with haematocrit reduction after 11 days at all doses. In the toxicology studies, haemodilution was observed across three tested species (rats, dogs, monkeys), with the effects most pronounced in dogs, while increased heart weight was seen in both rats and dogs studies, and cardiomegaly was evidenced as a substance-related malformation in the EFD study with rabbits. In light of these data, the possibility of elafibranor acting as a partial PPARγ agonist cannot be excluded from non-clinical data. However, the clinical data collected from Phase III studies of elafibranor (pivotal Study 319-1 and supportive Study 315-1) did not indicate PPARγ agonism.

Elafibranor showed no activity when screened against a panel of 13 nuclear receptors indicating its specific activation limited to the PPAR nuclear receptors. The 14 nuclear receptors were selected due to their relevance to liver diseases and their representation of different subgroups within the nuclear receptor superfamily. It can be agreed that investigating these 14 nuclear receptors allows for a reasonable generalisation of potential off-target effects.

Elafibranor but not its principal active metabolite GFT1007 was found to be a multiple but selective protein kinase inhibitor. The concentration used (10μM) in these studies is more than 500-fold higher than the expected maximal plasma concentration (Cmax) at the therapeutic dose of 80 mg elafibranor (0.0131μM). No inhibitory potency against TGFβR1 and TGFβR2 suggests that the mechanism of action of elafibranor in addressing fibrotic diseases may not involve direct inhibition of TGFβ1 receptor kinase activity. The selective inhibition of tyrosine protein kinases, including PDGFRβ, VEGFR1, VEGFR2, and FGFR 2, 3, 4—tyrosine protein kinases known for their involvement in hepatic fibrosis development—may play a role in elafibranor's anti-fibrotic activity. Nonetheless, challenges such as intra- and inter-assay variability, and a lack of clear understanding regarding the selectivity among tyrosine protein kinases prevent a definitive conclusion on whether the inhibition of specific kinases truly contributes to elafibranor's anti-fibrotic effects.

Significant safety margins were observed for the 22 kinases that showed >50% inhibition with elafibranor (10 μM) in the 300-kinase panel, at predicted human unbound C_{max}, there is a 66 to 1836-fold safety margin, depending on the kinase. High to very high margins of exposure are also seen in the rat ($\geq$364), monkey (39 to 1074) and rabbits ($\geq$1222). The most strongly inhibited kinase, PDGFRa still has a 66-fold safety margin in human, 364-fold in rat, 39-fold in monkey and 1222-fold in rabbit. This suggests that although kinase inhibition occurs *in vitro*, elafibranor concentrations remains within safe limits. The consistency of safety margins across different animal species supports the argument that the observed inhibition effects are not likely to lead to significant toxicities. The applicant emphasizes that the antifibrotic effects of elafibranor are more likely attributed to the activation of PPARα and PPARδ, rather than kinase inhibition. This can be agreed.

The main metabolite GT1007 did not exhibit inhibition of any kinases in a 15-kinase panel, while elafibranor inhibited 7 of them, indicating that GT1007 may not act as a kinase inhibitor, unlike its parent compound, at least on the tested kinases.

Since the clinical trials did not indicate off-targets effects, it can be agreed that inhibition of kinases might not play a significant role in elafibranor and GFT1007's mechanism of action or toxicity in any species.

In vitro safety pharmacology results showed that elafibranor and its main metabolites GFT1007 are not expected to affect cardiac repolarisation.

The effects of elafibranor on cardiac function were evaluated in a GLP-compliant study after single oral administration to conscious dogs. The applicant provided example graphs to indicate T wave morphology; did not provide ECG lead II data; provided 3 graphs from one animal at dose 100 mg/kg at 0, 1 and 20 hours as an example for 6-lead electrocardiogram. The applicant has deemed the data generated from the GLP study conducted at CERB (formerly ERBC) are reliable. These data were generated in accordance with the study plan, and the interpretation and conclusions drawn reflect the findings of the study. Therefore, these data can be considered to adequately assess elafibranor's potential effects on cardiovascular function.

It is noted that the effects of elafibranor on the cardiac function were evaluated in dogs, while in the toxicology section the applicant argues that dogs are not suitable non-clinical species due to their unique sensitivity to PPARα activation. Upon request the applicant has provided additional justification that dogs are most sensitive among non-clinical species to the PPAR agonists toxicity, making them unsuitable for the establishment of the safety margins, and that non-clinical testing for this type of substances is recommended to be conducted in rats and monkeys. However, the cardiovascular safety study which utilised a single dose administration, was conducted prior to the initiation of the repeated dose toxicity studies and did not reveal adverse effects which were observed in dogs upon prolonged elafibranor administration. This explanation is endorsed.

Under tested conditions, elafibranor demonstrated no adverse effects on the central nervous system. It did not show much negative impact on cardiac functions, except for the occurrence of tachycardia from 100 mg/kg. Respiratory function remained unaffected at doses of 30 and 300 mg/kg. However, at 1000 mg/kg (~165-fold clinical exposure, derived from exposures obtained in PK bridging rat study), elafibranor exhibited significant increases in peak inspiratory flow at 30 minutes after dosing and in tidal volume at 30 and 60 minutes after dosing, suggesting a respiratory stimulant action. Overall, the findings suggest a generally well-tolerated safety profile for elafibranor. However, higher dose of elafibranor shows respiratory stimulant action (1000 mg/kg) and increase heart rates (>30 mg/kg).

Pharmacokinetics

Clinical studies indicate that GFT3351 and GFT4775 are also major metabolites, even though the separate isomers of GFT4775 are not. Despite being inactive metabolites, they might induce off target effects. In addition, without any information on the toxicity of the different isomers, the different stereoisomers cannot be taken apart, since they might induce the same toxicity. According to the applicant, the expected accumulation ratio (AR) for GFT3351 and GFT4775 isomers can be predicted from terminal elimination rate constants (κ) determined in single-dose administration study in monkeys, indicating that only some accumulation might be expected for the parent compound, but not for the metabolites (including GFT1007). Without any repeated dose TK analyses for the metabolites, further calculations are only available based on single dose data. A comparison between plasma exposure levels in rats or monkeys and those in humans indicates that for each metabolite (GFT1007, [stereoisomers of] GFT3351 and [stereoisomers of] GFT4775], the exposure in at least one of the animals is at least 50% the exposure seen in humans. Therefore, it can be concluded that the characterisation of metabolite toxicity is considered adequate.

Only albino mice and rats were used in the tissue distribution studies. Melanin binding was neither analysed nor discussed by the applicant. However, the distribution study in monkeys (which do

produce melanin) shows no accumulation/retention in skin or eye, indicating no specific melanin binding. Since also the *in vitro* and *in vivo* phototoxicity studies conducted with elafibranor and/or GFT1007 were negative, further melanin binding studies are not needed.

Neither placental transfer studies, nor excretion studies in milk have been performed with elafibranor. However, in the rat PPND study, GFT1007 has been detected in 2 pups at LD14, suggesting that there may be some transfer from elafibranor and/or GFT1007 via placenta and/or milk. This finding and its consequences for use during pregnancy and breastfeeding has not been discussed. As outlined in 4.6 of the SmPC elafibranor should not be used during breast feeding.

The metabolite profile of elafibranor has been studies in several species, but not in rabbits, which are used in the reproductive toxicology studies. Although overall, metabolism seems to be relatively similar between species, there are some differences in the amounts of (major) metabolites that are observed (for example GFT3351 not being a major metabolite in rats, whereas it is a major metabolite in monkeys and humans). It is thus not clear whether elafibranor and its major metabolites (active and inactive) are sufficiently covered in the rabbit reproductive toxicity study. However, considering the proposed contraindication during pregnancy, this issue will not be further pursued.

Toxicology

Toxicity of elafibranor was investigated in the comprehensive battery of *in vitro* and *in vivo* studies. It is however noted that the achieved exposure levels in most toxicological studies were generally very low compared to the anticipated clinical exposure at MRHD, especially when elafibranor and its major metabolite GFT1007 are considered separately. Based on the exposure margins recalculated by the CHMP, the observed findings in the preclinical studies are likely to be clinically relevant, as most of the exposure margins for the repeat-dose toxicity studies for elafibranor are <1, although higher exposure margins were calculated for the FEED and EFD study in rats. For GFT1007, the exposure multiples in general appear to be higher than those of elafibranor. However, most are still <10.

It is further noted that in particular in rats a significant difference was found between the C_{max} and AUC values of elafibranor and GFT1007 in males and females (i.e., higher exposure of elafibranor in males and higher exposure of GFT1007 in females), suggesting a potential sex-related metabolic differences.

In repeated dose toxicity studies, elafibranor caused mainly adverse effects on the liver and RBC-related parameters across three species which were observed at clinically relevant exposure levels. Effects on liver generally consisted of increased liver weights accompanied by hepatocellular hypertrophy and multifocal single cell degeneration/ necrosis/ apoptosis of hepatocytes. In rats, also bile duct proliferation was noted. Markers of liver injury ALAT and ASAT were usually not increased, and the effects appeared to be largely reversible upon recovery. The effects on haematological parameters in dogs were very pronounced (up to 45% decrease in Hb, HCT and Hb levels at the top dose level of 300 mg/kg/day), whereas they were substantially milder in rats and monkeys. This effect is most likely caused by unique dog sensitivity to PPARα activation, and therefore dogs were not further pursued as test species.

Decreased cellularity and higher content of adipose tissue in bone marrow was reported in the monkey studies; however, this did not result in any appreciable bone marrow disfunction.

Some heart effects (increased heart weight, focal myocarditis) were observed in rats, but generally not in monkeys. The troponin I levels were not increased, and although there were some ECG changes (biphasic T-waves in males and reduced T-wave amplitude in females) seen in the 28-day monkey study, they were not observed in the 13- and 52-week studies. Increased heart weight, cardiac steatosis and increased troponin I levels were observed in the dogs at the top dose level; however, there were no corresponding ECG changes. Furthermore, appreciable increases of homocysteine levels (up to factor 3 increase) were seen consistently in rats and monkeys studies, however, without a

consistent dose- and time-dependent trend. Homocysteine levels have been investigated as a potential marker of cardiovascular events in clinical practice; however, based on the literature overview provided by the applicant, the evidence of correlation of increased homocysteine levels with cardiovascular disease appears to be contradictory. Overall, the results of non-clinical studies do not suggest high risk of cardiovascular toxicity of elafibranor, but it needs to be emphasised that the achieved exposure multiples are low, and thus potential clinical relevance of the observed effects cannot be ruled out based on non-clinical data.

It is worthwhile noting that the applicant claims that elafibranor is not a PPARγ activator, as it did not cause adverse effects normally associated with PPARγ activation, such as weight gain, haemodilution and cardiomegaly. However, binding of elafibranor to PPARγ receptors was demonstrated *in vitro* (refer to pharmacology section) and decrease of RBC-related parameters and (minor) cardiac effects were observed across all three tested species in repeated dose toxicity studies, while cardiomegaly, as well as other heart and great vessels malformations, was seen in the EFD study in rabbits (refer to developmental toxicity section). Overall, available evidence thus suggests that PPARγ activation by elafibranor is likely to occur at least to some extent.

It is interesting to note that, while pharmacological action of fibrates is usually associated with lowering the lipid levels, in particular triglycerides and cholesterol, this was not consistently observed for elafibranor. Furthermore, effects on certain clinical chemistry biomarkers, in particular ALP levels, cholesterol and bilirubin were also inconsistent between the species. In particular, cholesterol levels (both total and LDL cholesterol) were generally increased in rats and monkeys, while total cholesterol was decreased in dogs. Similarly, ALP levels were decreased in monkeys and increased in rats by elafibranor administration, while no effect on ALP levels was observed in dogs. Bilirubin was often decreased at the top dose levels in rats and monkeys, while no effect on bilirubin levels was seen in dogs. There was generally no appreciable effect on triglycerides, except in high-dose female rats in the 28-day study and all treated female rats in the 26-week study.

In primary biliary cholangitis, ALP levels increase with disease progression, as does bilirubin in more advanced disease, and together are both highly predictive of long-term clinical outcomes [Lammers 2014]. Furthermore, literature data suggest that ca. 75% of PBC patients are also presented with hypercholesterolemia (Wah-Suarez et al., Frontline Gastroenterol. 2019 Oct; 10(4): 401–408). Thus, it is important to elucidate influence of elafibranor on these biomarkers in different species and to compare it with the results observed in clinical trials, in order to establishing the species which can be considered most relevant to humans. Upon request the applicant has provided a detailed overview on the levels of 4 relevant biomarkers (ALP, total bilirubin, total and LDL cholesterol and triglycerides) in the non-clinical species upon elafibranor administration. Overall, in rats consistent and dose-dependent increases in ALP levels were seen across the studies, as well as decreases in bilirubin and increases in LDL cholesterol; however, the latter occurred without a clear relationship to dose levels and exposure duration. The ALP increases can likely be attributed to the known rodent sensitivity to PPARα agonist-induced peroxisome proliferation and are thus of low human relevance. In monkeys, on the contrary, dose-dependent decreases in ALP levels were observed in the repeated dose toxicity studies. No substantial effect on bilirubin levels was noted. A dose-dependent increase in total cholesterol was seen in the 52-week monkey study, reaching statistical significance at the top dose level, which was likely due to an increase in LDL-cholesterol. However, the levels returned to normal upon recovery. Decreases in ALP levels observed in monkeys are consistent with the lowered ALP levels reported in clinical studies.

With regard to genotoxicity, elafibranor was conclusively demonstrated to be clastogenic *in vitro*; however, it produced negative results in two *in vivo* micronucleus tests, as well as *in vivo* Comet assay and UDS test in liver. Adequate exposure to elafibranor was demonstrated by means of TK measurements. Based on this, elafibranor is considered non-genotoxic *in vivo*. Major metabolite

GFT1007 tested negative in the properly conducted Ames test and *in vitro* micronucleus test in mouse lymphoma cells; furthermore, exposure to GFT1007 was demonstrated in one of the *in vivo* micronucleus tests conducted with elafibranor. Available evidence is considered sufficient to conclude that GFT1007 is not genotoxic.

Metabolite GFT3351 tested negative in the properly conducted Ames test and in the *in vitro* micronucleus test in human lymphocites. It should be noted that GFT3351 is not formed as a major metabolite in rats, thus its genotoxicity *in vivo* is not considered to be covered by *in vivo* tests conducted with elafibranor in rats. However, the lack of genotoxic response in two GLP-compliant i*n vitro* tests does not suggest concern regarding potential genotoxic properties of GFT3351.

In the rat carcinogenicity study, elafibranor induced the "tumour triade" (hepatocellular carcinomas/adenomas and pancreatic acinar cell adenomas in both sexes and Leydig cell adenomas in males), as well as increased incidence of preputial gland carcinomas. In the mouse carcinogenicity study, increased incidence of hepatocellular carcinoma, adenoma and adenoblastoma at all dose levels was observed. The induction of the "tumour triade" in rats has previously been demonstrated for PPARα agonists; however, available evidence indicates that, while humans also possess a functional PPARα, they do not appear to be susceptible to PPARα agonists-induced oncogenesis. While the relationship of the increased incidence of the preputial gland carcinomas to elafibranor treatment cannot be excluded, these tumours are generally regarded as irrelevant to humans, as there is no human counterpart to the rodent preputial glands, and these glands are under different molecular regulation than other sebaceous or modified sebaceous glands making them inappropriate for biochemical modelling relative to humans. It should be noted that the achieved exposure multiples at the NOAEL were low (< 1 for elafibranor in both studies and GFT1007 in the mouse study and 2.8-13.6 for GFT1007 in the rat study, based on the AUC_{0-24}). However, higher sensitivity of rodents to PPAR activation compared to humans precludes the use of higher dose levels in the chronic study. Considering the lack of genotoxicity of elafibranor and the lack of hyperplastic/pre-neoplastic lesions in the 52-week monkey studies, elafibranor is not expected to present carcinogenic risk to humans based on the available data.

Elafibranor is not considered to show any appreciative adverse effects on fertility and early embryonic development. Minor effects on male fertility at the highest tested dose of 100 mg/kg/day seen in the first FEED study were not confirmed by the follow-up study in which treated males were mated with naïve females. Sufficient exposure multiples were achieved in the 2nd study at the NOAEL (26.8 for elafibranor and 36.6 for GFT1007 based on AUC0-24).

Embryo-foetal toxicity of elafibranor was evaluated in rats and rabbits. In rats, adverse effects on embryo-foetal development (increased post-implantation loss, decreased number of live foetuses and decreased mean foetal body weight) were observed only at a very high dose level of 1000 mg/kg/day causing significant maternal toxicity. In the study with rabbits, however, increased incidence of foetal malformations, primarily concerning heart and/or great vessels malformations, was seen at the top dose of 300 mg/kg/day. There were also two foetuses missing kidney and ureter. Additionally, there was an increased incidence of foetuses with structural malformations and variations, in particular malrotated paws or short tails, fused, misaligned or lower number of caudal vertabrae; misschapen or bent humerus, femur and tibia. These effects occurred in the presence of maternal toxicity. The NOAEL for developmental toxicity in rabbits is considered to be the lowest dose level of 30 mg/kg/day. This corresponds to very low exposure multiples (0.001 for elafibranor and 0.4 for GFT1007 based on the AUC_{0-24}), suggesting possible clinical relevance of the observed effects. However, known or suspected pregnancy is a contraindication for the treatment with elafibranor and adequate advice is included into the SmPC and PL.

It is noted that the applicant suggests that the effects seen in rabbits might be related to the profound change in lipid metabolism, as indicated by significant increase in cholesterol and triglyceride levels in maternal animals (+475% and +52%, respectively) at the top dose level. The applicant further speculates that such effects may not be relevant to humans, as predominantly reductions in cholesterol and triglyceride levels were seen in patients treated with elafibranor. However, as discussed in repeated dose toxicity section, no clear effect of elafibranor on cholesterol and triglyceride levels across different species could be established in the repeated dose studies; i.e. increase in total and LDL cholesterol was generally also seen in rats and monkeys (e.g. 61% and 50% increase in total cholesterol levels in 52-week monkey study in males and females, respectively) while dogs were the only species in which total cholesterol levels decreased upon elafibranor treatment. There was also no clear effect on triglyceride levels in any tested species (see further discussion in the repeated dose toxicity section). Also, no evidence has been provided by the applicant that changes in lipid metabolism in rabbits, in particular increased cholesterol and triglyceride levels, are known to cause foetal malformations in this species. As correctly stated by the applicant, there is thus no compelling evidence that the developmental toxicity seen in rabbits is irrelevant to patients. Considering very low exposure multiples at the NOAEL and severe adverse effects on pups seen in the PPND rat study, as discussed in the next paragraph, elafibranor is contraindicated during pregnancy and in women of childbearing potential not using an effective contraception.

In the GLP-compliant pre- and post-natal development study with rats, adverse effects on pup survival and development were observed already from the lowest tested dose of 10 mg/kg/day, corresponding to EM of 0.3 for elafibranor and 7.1 for GFT1007 at the LOAEL level based on AUC_{0-24}. The adverse effects were thus seen at clinically relevant exposure levels. These results differ significantly from the EFD study in rats where no adverse effects on pup survival were seen at the highest tested dose of 1000 mg/kg/day. Considering the negligible plasma levels of elafibranor and its metabolite GFT1007 in pups in the PPND study, as well as the fact that not only postnatal pup survival was reduced, but also the number of live born pups and dams with total litter loss were adversely affected by elafibranor treatment, it is considered not likely that the effects were caused by the exposure of the pups to elafibranor via maternal milk. Rather, it is more likely that the effects were caused by the dam exposure at the latest stage of pregnancy (GD17-GD23), as in the rat EFD study the treatment was stopped at GD17.

The applicant points out that the effects observed with elafibranor resemble the effects observed with another PPARα agonist fenofibrate, and the effects may thus be related to PPARα activation. Indeed, administration of fenofibrate at ca. 7 times the MRHD to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight at birth and on days 4 and 21 post-partum. However, fenofibrate was also clearly teratogenic in rats at ca. 10 times the MRHD when administered in the period of organogenesis (GD6-15), causing an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs). This is in stark contrast with elafibranor for which no teratogenic effects were seen in rats even at 26.8-fold MRHD. Rather, the pattern seen for elafibranor is similar to another fibrate, ciprofibrate, for which neonatal thrombosis was also reported in rat pups at clinically relevant exposure levels, while no teratogenicity was evident. Based on the observed effects and the absence of evidence that these effects are not relevant to humans, ciprofibrate is contraindicated in pregnancy. Therefore, contraindication in pregnancy for elafibranor is justified based on the available data, also taking into account its teratogenicity in rabbits.

The effects of elafibranor on juvenile animals were comparable with the effects in adult animals, with main effects seen on liver and RBC-related parameters which were seen already from the lowest tested

dose of 10 mg/kg/day. The long bone length was slightly reduced at 100 mg/kg/day. Juvenile males were apparently more sensitive compared to females, based on the more prominent effect on the RBC-related parameters which were not fully reversed upon recovery, and kidney toxicity, reflected as reduced urinary volume and increased specific gravity. In view of the significant difference between the C_{max} and AUC values of elafibranor and GFT1007 in males and females observed in the 13-week and 26-week repeated-dose studies (i.e., higher exposure to elafibranor in males and higher exposure to GFT1007 in females) and the different tolerance to elafibranor observed between young male and female rats, with males being more affected and taking longer to recover, the applicant was asked to discuss the possible impact of these potential sex differences on the safety and efficacy of the product under investigation. However, such differences in exposure between genders were not observed in other animal species. Moreover, no relevant gender effect was observed on the PK parameters of elafibranor and GFT1007 in an extensive Population PK analysis in human Phase III study patients. Therefore, no clinical impact is expected on the efficacy and safety profile of elafibranor between genders.

The PBT assessment is finalised: elafibranor is not PBT, nor vPvB. Elafibranor is not expected to pose a risk to the sewage treatment, the groundwater and sediment compartment.

The effects of elafibranor on juvenile animals were comparable with the effects in adult animals, with main effects seen on liver and RBC-related parameters which were seen already from the lowest tested dose of 10 mg/kg/day. The long bone length was slightly reduced at 100 mg/kg/day. Juvenile males were apparently more sensitive to the adverse effects on kidneys, based on the reduced urinary volume and increased specific gravity. Based on the effects on liver and RBC, the lowest tested dose level of 10 mg/kg/day is considered to be a LOAEL in this study, corresponding to exposure multiples of 0.8 and 0.1 for elafibranor and 12.5 and 15.0 for GFT1007 for males and females, respectively. It is noted however that PBC is not diagnosed in childhood, thus it is not expected that children will be treated with elafibranor.

Elafibranor is considered not to be PBT, nor vPvB. A risk to the STP, surface water, groundwater and sediment compartment is not anticipated based on the prescribed use of elafibranor.

2.5.7. Conclusion on the non-clinical aspects

The applicant has provided an extensive non-clinical data package.

Toxicological behaviour of elafibranor has been studied in the comprehensive package of *in vitro* and *in vivo* data. Elafibranor was found to cause malformations in rats and pup mortality in rats at levels below or comparable to the anticipated clinical exposure. Based on these observations, contraindication in pregnancy is warranted. Neither placental transfer studies, nor excretion studies in milk have been performed with elafibranor and adverse effects were seen in offspring when elafibranor was administered to female rats during pregnancy and lactation at clinically relevant exposure. Accordingly, a risk to the suckling child cannot be excluded and elafibranor should not be used during breastfeeding and for at least 3 weeks following last dose of elafibranor as outlined in 4.6 of the SmPC.

Elafibranor is not a PBT substance. Considering the above data, elafibranor is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

Tabular overview of clinical studies

Table 3: Clinical studies

Study Number	Study Design	Study Population (indication and number)	Key Objectives	Dose and Duration of Treatment	Study Status/Key Results
Completed Studies in PBC Indication: Key Efficacy and Safety					
Study 319-1	Phase III, double-blind, randomised, placebo-controlled study and open-label long term extension to evaluate the efficacy and safety of elafibranor 80 mg in patients with PBC with inadequate response or intolerance to UDCA	N=161 Elafibranor=108 Placebo=53	Efficacy, safety, PK	2:1 80 mg once daily for a minimum of 52 weeks or placebo; followed by an OLE up to 5 years [a]	Double blind part completed. OLE ongoing. For the primary endpoint statistically significantly higher proportions of patients in the elafibranor 80 mg group compared with placebo achieved cholestasis response at Week 52 (50.9% vs 3.8%); OR=37.56 [95% CI: 7.64; 302.25], p<0.0001. Statistically significant improvements in favour of elafibranor were also observed for the first key secondary endpoint (normalisation of ALP) at Week 52. A positive trend for improvement in pruritus was also observed through Week 52 with a greater reduction from baseline observed in the elafibranor 80 mg group compared with placebo in the PBC Worst Itch NRS. Elafibranor 80 mg was well-tolerated with a similar safety profile to placebo
Study 216-1	Phase II randomised, double- blind, placebo controlled, efficacy and safety study in patients with PBC and inadequate response to UDCA	N=45 Elafibranor 120 mg=15 Elafibranor 80 mg=15 Placebo=15	Efficacy, safety, PK	1:1:1 elafibranor 80 mg once daily, elafibranor 120 mg once daily or placebo; 12 weeks	Study complete. In both elafibranor-treated groups, a significant decrease in mean ALP at 12 weeks was achieved: -48% for the 80 mg dose and -41% for the 120 mg dose, compared to a mean 3% increase in ALP in patients receiving placebo. This demonstrated a highly

					significant relative reduction of ALP for elafibranor versus placebo: -52% (95% CI: [-62.5; -41.5], p<0.001) for 80 mg and -43.9% (95%CI: [-55.7; -32.1], p<0.001) for 120 mg elafibranor. Elafibranor 80 mg and 120 mg were well tolerated with a similar safety profile to placebo.
Ongoing Study in PBC Indication					
Study 454	Phase III, multicentre, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of elafibranor 80 mg on long-term clinical outcomes in patients with PBC and inadequate response to UDCA	Planned: N=450 Elafibranor 80 mg=300 Placebo=150	Efficacy, safety, PK	2:1 80 mg once daily or placebo once daily for up to approximately 84 months	Not applicable - ongoing

ALP=alkaline phosphatase; CI=confidence interval; N=number of patients treated OLE= open-label extension; OR =overall response; PBC=primary biliary cholangitis; PK=pharmacokinetics; QD=once daily; UDCA=ursodeoxycholic acid; [a] The open-label extension period is ongoing; only efficacy data from the double-blind period are included.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

A total of 18 completed clinical pharmacology studies have been conducted in support of elafibranor. The pharmacokinetics were investigated of elafibranor and its major active metabolite GFT1007. The clinical pharmacology component of the current submission relies heavily on the historical package generated originally in support of the NASH and metabolic disorder programme that was later terminated due to lack of efficacy. The applicant has undertaken a final PopPK analysis, using available PK data for elafibranor from all prior relevant clinical studies, including the data from the phase II and phase III studies in PBC and NASH.

Elafibranor and GFT1007 were analysed in plasma and urine using validated LC-MS/MS assays. Overall, full validations were carried out according to the "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217 /2009 Rev.1 Corr.2) in force when the trials and relevant PK analyses took place. The analytical methods were sufficiently validated.

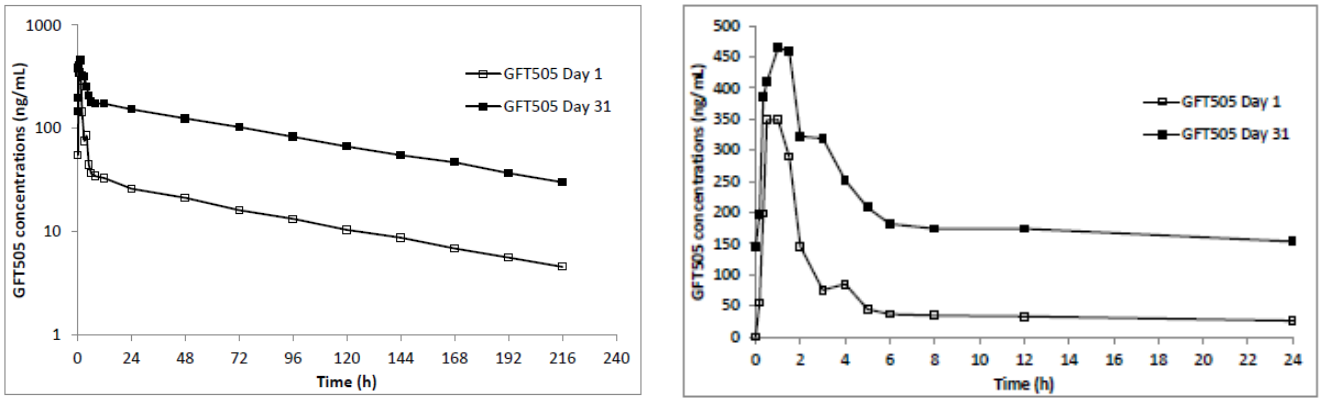
Absorption

In the food effect study (study 452), a single dose of 80 mg (the commercial formulation, formulation 6) was administered to healthy male and female subjects (n=33). Median peak plasma levels of elafibranor and GFT1007 occurred at 1.5 – 2.0 h and at 1.5 – 2.5 h respectively (overall both fasted and fed state). Over all studies with single dose, with doses up to 300 mg, median peak plasma levels of elafibranor and GFT1007 occurred within 0.5 to 3.0 hours and within 1.0 to 3.0 hours, respectively.

Elafibranor is absorbed via a sequential zero-order and first-order process after a short lag time and its disposition follows a two-compartment kinetic process with linear first-order elimination. Absorption of elafibranor appears highly variable and erratic as can be observed in individual overlaid concentration-versus-time plots. Interindividual variability (CV%) in study 216-1 (phase II study, see further below) (single and repeated dose administration of 80 or 120 mg to patients with PBC) for C_{max} was 44.9% to 65.4% for elafibranor and 31.6% to 55.2% for GFT1007. For AUC the variability ranged from 64.6% to 84.0% for elafibranor and 35.8% to 46.5% for GFT1007.

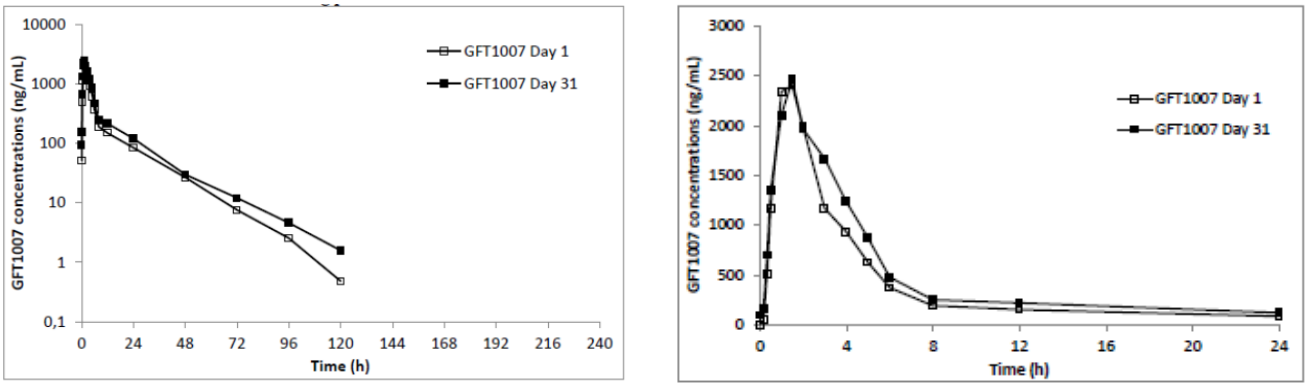
In the food effect study (study 452, healthy subjects), within-subject coefficient of variation for C_{max} was 63.3% for elafibranor and 29.3% for GFT1007. For AUC the within-subject CV was 15.5 – 15.7% for elafibranor and 9.7 – 12.8% for GFT1007. Given the within-subject CV for C_{max} for elafibranor, this product can be classified as a highly variable compound.

In study 115-12, 120 mg/day was administered for 16 days to healthy male subjects (n=12). Concentration-time profiles of elafibranor and GFT1007 after single and repeated dose administration are shown in figures below.



Data Source: Study 11512 Figure 11.3.1.11.
Note: Single dose on Day 1; QD dosing from Day 16 to Day 31.

Figure 2: Mean elafibranor plasma concentrations after a single and 16 day repeated oral elafibranor administration at 120 mg in healthy male participants (semi log on the left, linear 24-h plot on the right) (study 115-12 part 3)



Data Source: Study 11512 Figure 11.3.1.12.
Note: Single dose on Day 1; QD dosing from Day 16 to Day 31.

Figure 3: Mean GFT1007 plasma concentrations after a single and 16 day repeated oral elafibranor administration at 120 mg in healthy male participants (semi log on the left, linear 24-h plot on the right) (study 115-12 part 3)

In a phase II study in subjects with PBC (target population), elafibranor (formulation 5) was administered at 80 mg or 120 mg for 12 weeks. PK parameters were determined on the first day and after 2 weeks. After repeated administration of 80 mg/day for 2 weeks, median peak plasma levels occurred at 1.0 (0.5 – 2.0) hours and 1.3 (0.5 – 2.0) hours respectively. Over all studies with repeated administration with doses up to 300 mg, median peak plasma levels of elafibranor and GFT1007 occurred within 0.500 to 3.00 hours and within 1.00 to 2.00 hours, respectively.

Table 4: Elafibranor and GFT1007 pharmacokinetic parameters (mean±sd) after single and repeated administration to subjects with pbc (study 216-1)

Analyte	Treatment group (Elafibranor dose)	N	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_t (ng•h/mL)	AUC_{24} (ng•h//mL)
Single administration						
Elafibranor	80 mg	13	611±274	0.500 (0.250; 2.00)	1188±998	1293±999
	120 mg	12	644±421	1.00 (0.250; 2.00)	1525±984	1665±976
GFT1007	80 mg	13	2127±713	1.00 (0.500; 2.17)	9491±4213	9497±4077
	120 mg	12	2684±848	1.50 (1.00; 2.00)	12149±4351	12131±4339
Repeated administration						
Elafibranor	80 mg	14	802±443	0.975 (0.500; 2.00)	3764±1748	3758±1749
	120 mg	13	793±389	0.500 (0.250; 1.50)	4418±1800	4394±1787
GFT1007	80 mg	14	2058±459	1.25 (0.500; 2.00)	11994±7147	11985±7149
	120 mg	14	2757±1359	1.00 (0; 6.00)	14145±5742	14135±5743

AUC_t=area under the concentration time curve from time zero to time t; AUC_{24}=area under the concentration time curve from time zero to 24 hours; C_{max}=maximum plasma drug concentration; N=number of participants; SD=standard deviation; t_{max}=time to reach maximum plasma drug concentration following drug administration.
Data Source: Study 216-1 Analytical and PK Report Amendment 1 (04 April 2019).
Note: For participants for whom the last available concentration was before the 24 hour timepoint, AUC_{24} was extrapolated.
[a] t_{max} presented as median (min–max).

Absolute bioavailability

The absolute bioavailability of elafibranor has not been determined in humans, given its low solubility at physiologically relevant pHs, which was considered to result in significant challenges in the formulation of a clinically suitable intravenous formulation for elafibranor even at very low concentrations.

Regarding the BCS classification, although *in vitro* permeability of elafibranor was high, there is no *in vivo* study with intravenous administration and therefore high bioavailability *in vivo* cannot be verified. Moreover, elafibranor is a substrate of MRP2 and BCRP. The applicant provided sufficient information on the in-vitro solubility of elafibranor for BCS Class II or IV classification.

Bioequivalence / relative bioavailability

Six different immediate release formulations of elafibranor have been used in clinical studies of elafibranor (4 capsule and 2 tablet forms):

- Formulation 1 was a 5 and 10 mg capsule;
- Formulation 2 was a 5 and 20 mg capsule;
- Formulation 3 was a 60 mg capsule;
- Formulation 4 was a 40 mg capsule;
- Formulation 5 was an 80 and 120 mg tablet;
- Formulation 6 was an 80 and 120 mg tablet.

Formulations 1 to 4 have been used for the NASH indication clinical development. The applicant is intending to commercialise an 80 mg immediate release film-coated tablet (formulation 6) in support of the PBC indication. Formulation 5 is the same as the commercial elafibranor 80 mg film-coated tablet, with the exception of a slightly different composition of the coating agent.

The provided results of the bioequivalence study comparing Formulation 5 and 6, and the bioavailability studies comparing several formulations provide support that use of any of the

formulations in clinical studies, whether it is tablet or capsule, will result in similar systemic exposure to both elafibranor and GFT1007.

Influence of food

Phase I study 452 was conducted to pivotally evaluate the food effect on the bioavailability of elafibranor and its active metabolite GFT1007 following 80 mg tablet single oral administration. Food effect was investigated also in study GFT505-106-1. Both studies' results are consistent between each other. Study 452 was a pivotal high-calorie food effect study conducted with the commercial elafibranor 80 mg tablet formulation. This study revealed that there was a slight delay in t_{max} of both elafibranor and its active metabolite GFT1007, which was consistent with the expected delayed gastric emptying. Whilst there was a 48% and 28% reduction in C_{max} observed for elafibranor and GFT1007, respectively, in the fed condition, there was limited or no impact on overall exposure (AUC) of elafibranor (1596 versus 1374 ng×h/mL) and GFT1007 (7024 and 7040 ng×h/mL) under fasted or fed conditions. Hence, the intake of food is not expected to have clinically significant consequences to the efficacy profile of elafibranor. Given that the food effect study demonstrated a decrease in C_{max} and no increase in overall plasma exposure for either elafibranor or GFT1007, no increase in the safety risk is expected.

Distribution

Mean plasma *in vitro* protein binding of both elafibranor and GFT1007 is 99.7%, at concentrations around 500 ng/mL for elafibranor and 2500 ng/mL for GFT1007, i.e. at concentrations comparable to the C_{max} at steady state. There was no or limited effect of severe renal impairment and mild or moderate hepatic impairment on protein binding. Severe hepatic impairment led to an approximately 2- and 2.7-fold increase of the unbound drug exposure of the parent and active metabolite, respectively. Elafibranor and its main metabolites distribute preferentially to plasma and not to blood cells (total radiocarbon mean plasma C_{max} and AUC_t were approximately 1.9- and 2.4-fold higher than in whole blood). Mean apparent volume of distribution (Vd/F) following a single 80 mg dose in healthy subjects was 4731 - 5389 L. This indicates distribution beyond the plasma compartment.

Elimination

Following a single dose of 120 mg of 14C-labelled elafibranor, 77.1% was excreted in the faeces and 19.3% in the urine. In the faeces, the major part was excreted as elafibranor (57% of dose). Elimination half-life in healthy subjects under fasting conditions was 68 h for elafibranor and 15 h for GFT1007. The shorter half-life of GFT1007 is considered to be due to high first-pass metabolism of elafibranor in the enterocytes and slow elimination of elafibranor from the systemic circulation. CL/F of elafibranor under fasting conditions was 50.0 L/h.

Elafibranor and GFT1007 were not metabolised by CYP enzymes or by UGT enzymes to a clinically relevant extent. Metabolism of elafibranor into GFT1007 by prostaglandin reductase 1 (PGR1) was a major pathway in vitro. In vivo, elafibranor is metabolised to the major active metabolite GFT1007, to the major inactive metabolites GFT3351, which is an acyl glucuronide present as 4 stereoisomers, and GFT4775 and to several minor metabolites. After single dose administration of 120 mg to healthy subjects, elafibranor comprised 13% of total exposure in plasma, GFT1007 46%, GFT3351 29% and GFT4775 13%. Metabolic pathways are shown in **Figure 4**.

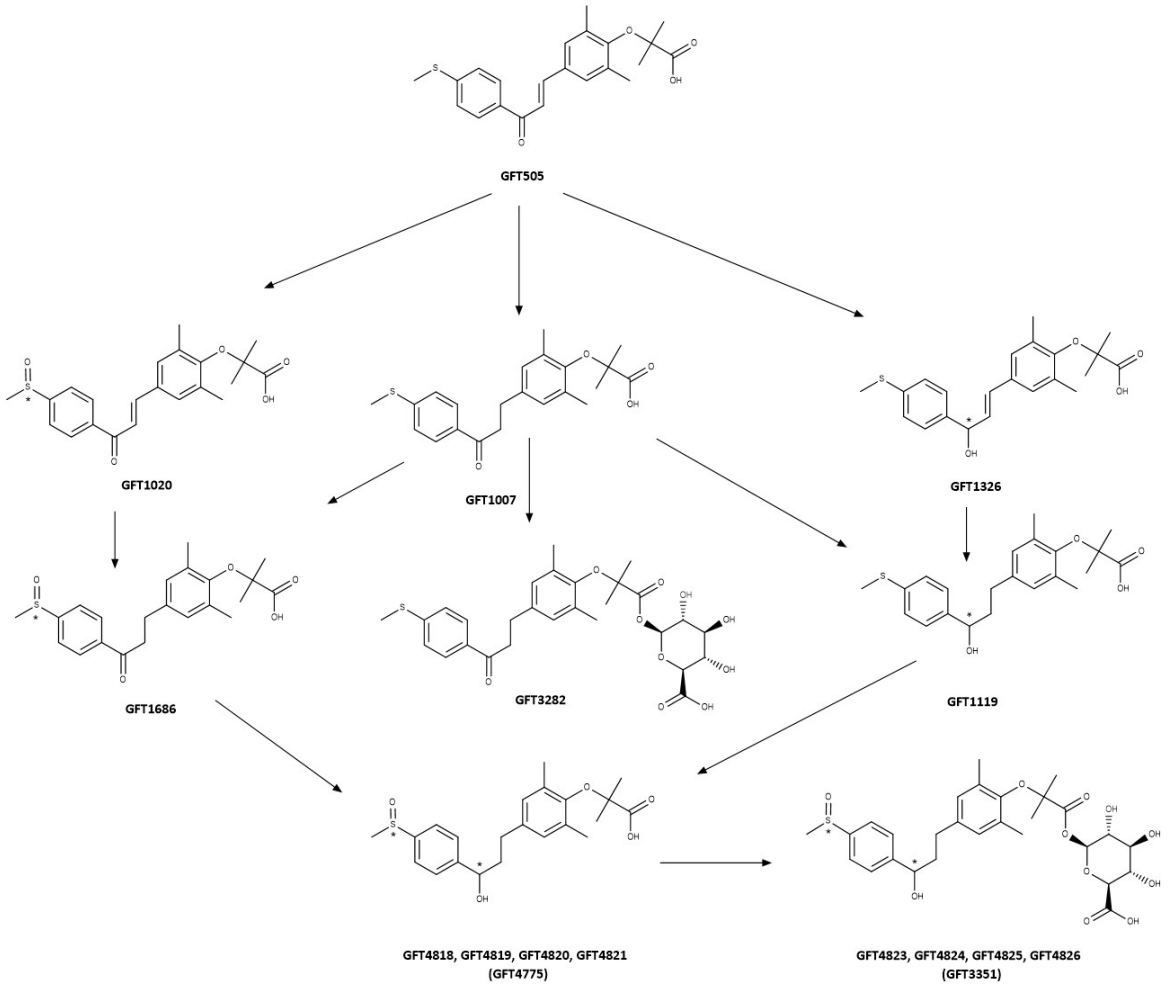


Figure 4: Proposed metabolic pathways of elafibranor in humans

Population-based pharmacokinetic (PopPK) modelling

The aim of the population-based pharmacokinetic (PopPK) modelling was to characterise the population pharmacokinetics of both elafibranor and the active metabolite, GFT1007, and to derive exposure metrics for PK/PD analyses leveraging PK data from 17 clinical studies (13 Phase I studies, 2 phase II studies, and 2 Phase III studies) in healthy subjects, patients with renal impairment, participants with hepatic impairment, patients with NASH, and patients with PBC. The primary PK parameters considered are all absorption and disposition parameters in the final model. The secondary PK parameters considered are the 24-hour area under the concentration-time curve during a dosing interval at steady state ($AUC_{\tau,ss}$), maximum concentration during a dosing interval at steady state ($C_{max,ss}$), and minimum concentration during a dosing interval at steady state ($C_{min,ss}$). The population and individual pharmacokinetics of elafibranor and GFT1007 were described using two separate 2-compartments disposition models with a sequential zero and first order absorption model with lag time and a linear elimination. A simultaneously estimated joint model was not pursued due to runtimes up to the order of weeks. It is however deemed questionable if it would not have been better to select a smaller, potentially more relevant, dataset through which runtimes could have been shorter and simultaneous estimation could have been possible.

The final elafibranor and GFT1007 PK models included various covariate-parameter relationship including allometric scaling of body weight (WT) on CL and V parameters, age, formulation and food effects, and renal and hepatic function. Both models also included several inter-individual variability (IIV) and residual unexplained variabilities (RUV) values. Remarkable is the impact of the type of

bioanalytical methods in the final elafibranor model, where it is high and has the largest effect on all the secondary elafibranor PK parameters (exposure metrics).

Although the analysis has been carried out using the best available technology and practice, the conclusions should be interpreted with caution. In fact, as also acknowledged by the applicant, the analysis has certain limitations, and the models have misspecifications. In particular, some of these problems are related to the data set (it includes records collected from many different studies and conditions), others to computational limitations associated with the development of complicated models involving numerous covariate-parameter relationships, and still others to statistical assumptions (e.g. normality of distributions in Forest plots).

Dose proportionality and time dependencies

Based on two clinical studies, dose proportionality in the exposure to elafibranor and its main metabolite could be concluded within the dose range of 10-70 mg and 120-240 mg, respectively. The popPK analysis encompassing all PK data available showed that dose-proportionality has been sufficiently justified for dose levels beyond 50 mg.

Approximate steady state was reached by 14 days (5x $t_{½}$ of elafibranor). The accumulation ratio for AUCτ was 3.6 for elafibranor and 1.3 for GFT1007, following once daily dosing. This is consistent with the longer apparent terminal $t_{½}$ of elafibranor (68.7 hours) compared to GFT1007 (15.4 hours). No time dependency in the pharmacokinetics of elafibranor nor GFT1007 was detected in healthy volunteers that were dosed up to 16 days.

Target population

One phase II and one phase III study have been performed in patients with PBC. Study 216-1 was a proof-of-concept study (phase II) to evaluate the efficacy of elafibranor 80 mg and 120 mg up to 12 week in subject with PBC, measuring the relative change from baseline in serum ALP levels as a primary endpoint, while study 309-1 was a phase III study in PBC patients administered with 80 mg up to 52 week. Intensive blood sampling for PK analysis was done in study 216-1 and results suggest that the PK of elafibranor and GFT1007 are not modified in subjects with PBC as compared to healthy subjects.

Special populations

PopPK analysis was used to identify subject characteristics as covariates affecting the PK of elafibranor and GFT1007 based on their relevance on model parameters.

Also dedicated studies were performed in subjects with renal (end stage renal disease) and hepatic impairment (Child-Pugh classification A, B and C). Overall, data from the renal impairment study suggest that there is a minimal effect of renal function on exposure to unbound and total elafibranor (decrease of about 22% and 33% in AUC_{inf}, respectively). In the proposed SmPC it is reported that "No dose adjustment is necessary in patients with renal failure" in section 4.2 and that "there is no evidence that age (18 to 80 years), gender, race, body mass index and kidney status had a clinically significant impact on Elafibranor and GFT1007 PK" in section 5.2. However, results from forest plots obtained from the popPK analysis showed that estimated glomerular filtration rate (eGFR) at baseline was found to be a relevant covariate on the clearance model parameter, but only for the metabolite GFT1007 PK model. Renally impaired patients with creatinin clearance of 15 mL/min/1.73 m^2 have ~30% increased $AUC_{\tau,ss}$ and ~60% increased $C_{min,ss}$ compared to healthy subjects. However, overall, the collected evidence, both empirical and simulated, suggests that exposure to elafibranor and GFT1007 is not clinically different between patients with either impaired or normal renal function.

Based on the results from an open-label, phase 1, single dose study 118-14 after administration of elafibranor 120 mg in adults with hepatic impairment and healthy subjects, the non-recommendation

of use in patients with severe hepatic impairment (Child-Pugh C) is supported (sentences reported in section 5.2 and 4.2 of the SmPC are considered acceptable). Hepatic impairment was not identified as statistically significant predictor for the PK of elafibranor and GFT1007 in the popPK analysis.

The effect of gender was evaluated in the context of study 111-7- part 1. The exposure in female participants was 20-25% lower than in male participants at 120 mg for elafibranor and GFT1007, which is not considered clinically relevant (study 111-7 Part 1). Furthermore, in study 111-7 Part 2 and 3, the objective was to determine tolerability and PK of single and multiple ascending oral doses of elafibranor in overweight or obese male participants (BMI between 28 and 35 kg/m^2). After a single 120 mg dose of elafibranor under fasted conditions, the mean AUC_{24} exposure to elafibranor and GFT1007 was approximately 37% and 18% lower, respectively, in otherwise healthy overweight participants than in normal weight participants (BMI range 20–26 kg/m^2).

Open-label, phase 1, single-dose study 119-16 was conducted to evaluate the PK of elafibranor 120 mg in healthy elderly and young adult volunteers. The drug exposure to the active metabolite GFT1007 was found to be 50% higher in the elderly population (75-80 yrs) as compared to young adults of 18-45 yrs. Yet in the PopPK study no relevant age effect was observed on the PK parameters of elafibranor and GFT1007, thus no dose adjustment appears required based on age. The claimed indication is not diagnosed in children. However, CL/F and Vd/F are similar between the healthy elderly and young adults, so the reason for this increased exposure in elderly subjects is not clear. No clear information has been reported in the SmPC regarding these increased exposures. In section 4.2 it is reported that no dose adjustment is needed in elderly patients, while in section 5.2 data from popPK analysis have been reported under Special populations: There was no evidence that age (from 18 to 80 years old), gender, race, Body Mass Index and renal status, had any clinically meaningful impact on elafibranor and GFT1007 PK. DataD from study 119-16 and data from the popPK report are not aligned. The popPK model showed that the effect of age on elafibranor and GFT1007 PK was statistically significant, but not clinically relevant. GlomerularG filtration rate was quantified differently across different studies (using absolute GFR/CLCR or estimated GFR adopting either the MDRD formula or the CKD-EPI formula).

Limited information is still available on the influence of race as the majority of the PK population consisted of white subjects (N=757) and 20 subjects were black. Exposure to elafibranor tended to be maximally 16% higher in Japanese subjects as compared to non-Asian subjects (all white), which is considered to be not clinically relevant. Exposure to GFT1007 tended to be somewhat lower in Japanese subjects, to a maximum of 10%.

Pharmacokinetic interaction studies

Elafibranor and GFT1007 as substrate

Elafibranor is a substrate of MRP2 and BCRP, which is however found to be not clinically relevant because passive permeability in a Caco-2 cell model was high, indicating that passive, concentration-gradient driven, absorption of elafibranor will already be high and the effect of inhibition of MRP2 and/or BCRP will not be clinically relevant. GFT1007 was not a substrate of the investigated transporters (see below). Elafibranor and GFT1007 are not substrates to a relevant extent of CYP enzymes or UGT enzymes. Elafibranor is a substrate of PGR1 *in vitro*.

Effects of elafibranor and GFT1007 on the PK of other drugs

In vitro studies indicated no clinically relevant inhibition or induction of CYP enzymes by elafibranor or GFT1007 and no clinically relevant inhibition of CYP enzymes by GFT3351. Elafibranor and GFT3351 did not inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B10 and UGT2B15 to a clinically relevant extent *in vitro*. GFT1007 inhibited UGT1A6 (IC50 value of 1.53 µM is below the systemic cut-off value for GFT1007 of 2.66 µM), but did not inhibit UGT1A1, UGT1A3, UGT1A4,

UGT1A9, UGT2B7, UGT2B10 and UGT2B15 to a clinically relevant extent. There are not many UGT1A6 substrates with glucuronidation as major pathway. Inhibition of UGT1A6 is therefore not expected to be clinically relevant. In vitro inhibition was observed of OATP1B3 and BCRP by elafibranor. Elafibranor did not inhibit P-gp, OATP1B1, OAT1, OAT3, OCT2, OCT1, MATE1, MATE2 and BSEP to a clinically relevant extent. GFT1007 and GFT3351 did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE1, MATE2, BSEP and MRP2 (only investigated for GFT3351) to a clinically relevant extent.

In vivo DDI studies are shown below. In vivo, no significant effect of indomethacin on C_{max} or AUC_{inf} of elafibranor and GFT1007 was observed. In vitro, human recombinant prostaglandin reductase 1 (PGR1) was shown to catalyse the transformation of elafibranor into GFT1007, with NADPH as the main cofactor, and the NADPH-dependent metabolisation of elafibranor by hrPGR1 was inhibited by indomethacin. Since *in vivo* no inhibition by indomethacin (at a clinically relevant dose) was observed, no clinically relevant interaction through inhibition of PGR1 is therefore considered to occur.

Slight decreases, which were not clinically relevant, were observed in the exposure to simvastatin and atorvastatin following co-administration with elafibranor. No clinically relevant inhibition of OATP1B3 or BCRP or induction of CYP3A4 is therefore expected to occur. No inhibition of warfarin following co-administration with elafibranor was observed. Elafibranor is therefore considered not an inhibitor of CYP2C9.

Table 5: Summary of clinical DDI studies (substance ratios as percent with 90% confidence intervals)

Comparison	Substance Ratio, as Percent (90% CI)		Dosing Recommendation
	C_{max}	AUC_{inf}	
Victim			
Effect of co-administration with indomethacin (PGR1 inhibitor) (study 119-15)	Elafibranor: 89 (69, 116) GFT1007: 98 (89, 108)	Elafibranor: 90 (83, 98) GFT1007: 100 (93, 108)	No adjustment
Effect of co-administration with simvastatin (study 109-5)	Elafibranor: 77 (59, 100) GFT1007: 91 (76, 109)	Elafibranor: 106 (99, 115) GFT1007: 107 (103, 113)	No adjustment
Perpetrator			
Effect on simvastatin (substrate of OATP1B3 and BCRP) (study 109-5)	Simvastatin: 64 (44, 93) Simvastatin β-hydroxyacid: 74 (62, 88)	Simvastatin: 99 (80, 123) Simvastatin β-hydroxyacid: 68 (54, 86)	No adjustment
Effect on warfarin (substrate of CYP2C9) (study 112-8)	R-warfarin: 96 (89, 102) S-warfarin: 96 (89, 131)	R-warfarin: 98 (95, 101) S-warfarin: 96 (93, 99)	No adjustment
Effect on atorvastatin (substrate of OATP1B3 and BCRP) (study 115-11)	72 (60, 87)	AUC_{0-72h}: 88 (82, 93)	No adjustment

Pharmacokinetics using human biomaterials

The solubility of elafibranor has been determined to be low with a solubility lower than 0.32 mg/mL at 37 °C in the pH range of 1 to 6.8. In vitro permeability assays in Caco-2 cells showed high permeability for elafibranor tested at 0.4 – 10 µM compared to high permeability standard minoxidil (($P_{app\ A-B}$ 13–17 x 10^{-6} cm/s for elafibranor vs 5.3 x 10^{-6} cm/s for minoxidil). Elafibranor $P_{app\ B-A}$ was higher than $P_{app\ A-B}$ (38 – 54 x 10^{-6} cm/s vs 13 – 17 x 10^{-6} cm/s in the absence of inhibitors). In the presence of inhibitors, $P_{app\ A-B}$ was higher than $P_{app\ B-A}$. In vitro, elafibranor was found to be a substrate of the intestinal efflux transporters MRP2 and BCRP. GFT1007 was not a substrate of MRP2 and BCRP. Elafibranor and GFT1007 were not substrates of OATP1B1, OAT1B3, OAT1, OAT3, OCT2, P-gp, MRP3, OATP1A2 and OATP2B1.

2.6.2.2. Pharmacodynamics

Mechanism of action

Elafibranor and its main active metabolite GFT1007 are dual peroxisome proliferator-activated receptor (PPAR)α/δ agonists.

Activation of PPARα decreases bile acid (BA) synthesis, increases BA detoxification, and modulates BA output.

Activation of PPARδ also regulates transporters that absorb and secrete bile components, contributing this way to decreased bile toxicity and improving cholestasis.

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

Primary and secondary pharmacology

No separate information on pharmacodynamics was provided. The most important pharmacodynamic effects are studied in the phase III study (319-1) either as primary or secondary endpoint. A notable and consistent decrease from baseline at week 52 in total cholesterol was reported. The main contributors for those decreases were significant reductions in TGs and VLDL-C, and to a lesser extent reductions in LDL-C, while HDL-C remained stable.

Effect on QT interval

Phase I, two-parts, study 113-9 was conducted in healthy subjects to evaluate the effect of elafibranor on the measured QT interval/corrected QT (QTc) interval. Part 1 evaluated the safety and tolerability of two dose levels of elafibranor (300 and 360 mg) after multiple dose administration once daily for 14 days, in order to determine the supra-therapeutic dose to be administered in the TQT trial (Part 2). Part 2 evaluated the impact on QTcF (QT interval after Fridericia's correction of measured QT interval) of therapeutic (120 mg) and supra-therapeutic (300 mg) doses of elafibranor, after multiple dose administration once daily for 14 days compared to placebo and a positive control (moxifloxacin 400 mg, single oral dose). As secondary objective, Part 2 investigated the impact of such two dose levels on QTcB (QT interval after Bazett's correction of measured QT interval).

24 volunteers were included in Part 1 (cohort 1: 9 subjects received elafibranor 300 mg/die and 3 placebos; cohort 2: 9 subjects received elafibranor 360 mg/die for 14 days and 3 placebo). 176 volunteers were included in Part 2: placebo group (n=42), elafibranor 120 mg (n=42), elafibranor 300 mg (n=47), moxifloxacin (n=45). The QT/QTc Analysis Set included all the subjects who completed the study with fully available 24 h-holter ECG data (n=168).

Analysis of holter ECG collected during Part 1 did not point out any clue suggesting that multiple oral administration of GFT505 up to 360 mg could lead to relevant prolongation of QT interval or, more generally, could impact cardiac activity as expressed by ECG parameters. Moreover, as shown by results obtained from the Study Part 2, the upper limit of the 90% CI of the estimated changes from baseline and placebo (ΔΔQTcF) did not exceed 1.7 ms with GFT505 120 mg and -1.7 ms with GFT505 300 mg at any of the measured time-points, well below the predefined margin of 10 ms, thus excluding any effect of GFT505 on QT/QTc interval at both therapeutic and supra-therapeutic doses.

Pharmacokinetics/Pharmacodynamics

PK/PD exposure-response modelling was performed to investigate the relationship between the PK of elafibranor and its metabolite GFT1007 and 4 efficacy endpoints (ALP, total bilirubin (TBIL), PBC score and Worst Itch Numeric Rating Score (WI-NRS) for pruritus) following oral administration in adult patients with PBC. These exposure-response (ER) models showed that some significant drug effect could be captured. For pruritus score this was not possible since there was no distinguished drug effect from placebo effect.

A joint ALP-TBIL model was developed to characterize the relationship between the PK of elafibranor (elafibranor and GFT1007) and PD (ALP and TBIL) in adult PBC patients. The joint model had similar parameter estimates compared to the separate ALP and TBIL models. The main joint ALP-TBIL model provided a sufficient description of both the ALP and TBIL data.

The sum of the areas under the concentration-time curve during a dosing interval at steady state of elafibranor and GFT1007 ($AUC_{\tau,ss\ sum}$) predicted by the final popPK models was used as a driver for drug effects on ALP, TBIL, PBC score, and pruritus score. According to the applicant, other PK metrics were not evaluated since the drug effects were already well characterized using $AUC_{\tau,ss\ sum}$ and the PD observations are sparse relative to the turnover of the PK of elafibranor and GFT10071.

However, it was noted from **Figure 5** that the median $AUC_{\tau,ss\ sum}$ for the 80 and 120 mg/day treatment groups are 32.3 µmol·h/L and 39.3 µmol·h/L, respectively, which implies only a 1.2-fold increase in total exposure upon a 1.5-fold increase in elafibranor dose. The applicant was requested to explain and discuss the consequences of this apparent disproportionality in total PK of elafibranor plus GFT1007.

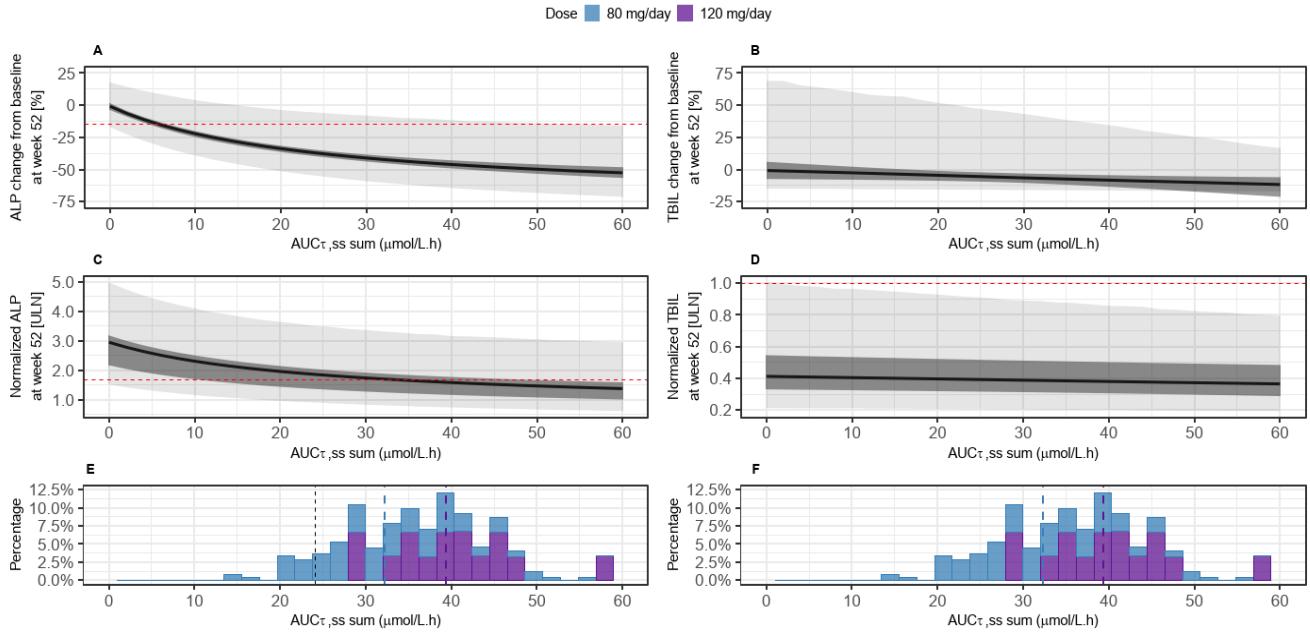


Figure 5: Simulated relative alp change from baseline, normalised alp, relative TBIL change from baseline, and normalised TBIL versus the $AUC_{\tau,ss\ sum}$ and distribution of the $AUC_{\tau,ss\ sum}$ by dose

Note: Relative ALP change from baseline (A), normalised ALP (C), relative TBIL change from baseline (B) and normalised TBIL (D) at week 52 versus the $AUC_{\tau,ss\ sum}$ based on the simulation of 100,000 typical parameter sets with uncertainty but without IIV (median and 90% CI depicted by black lines and dark grey ribbons, respectively) and the simulation of 100,000 virtual participants including IIV (90% PI depicted by light grey ribbons).
The distribution of the $AUC_{\tau,ss\ sum}$ is also shown for the Full Resampled Analysis Set (E,F). The distribution of the $AUC_{\tau,ss\ sum}$ is coloured by dose. The red dashed lines represent the thresholds for the relative ALP change from baseline, normalised ALP and normalised TB at 15% (A), 1.67·ULN (C) and ULN (D), respectively. The black dashed line (E) represents the $AUC_{\tau,ss\ sum,50}$, and the blue and violet dashed lines represent the median of the $AUC_{\tau,ss\ sum}$ in the 80 and 120 mg/day treatment groups, respectively (32.3 µmol·h/L for the 80 mg/day group and 39.3 µmol·h/L for the 120 mg/day group).

The applicant responded that this apparent disproportionality can be explained by differences between the 80 mg/day and the 120 mg/day patient groups, as the 80 mg/day and the 120 mg/day patient groups differ in median body weight (120 mg/day group had 14% higher median body weight), which could explain the less than dose proportional difference in AUC, but this is not expected to have affected dose-response conclusions.

When participants from both dose groups are pooled and each participant is included in both the 80 mg/day and in the 120 mg/day group, the expected 1.5-fold increase from a dose of 80 to 120 mg/day is obtained with medians of 31.45 and 47.18 in 80 mg and 120 mg groups, respectively. **Figure 6** seems to suggest that the included population for the 120 mg/day treatment is smaller than for the 80 mg/day treatment even though the analysis contains a pooled dataset.

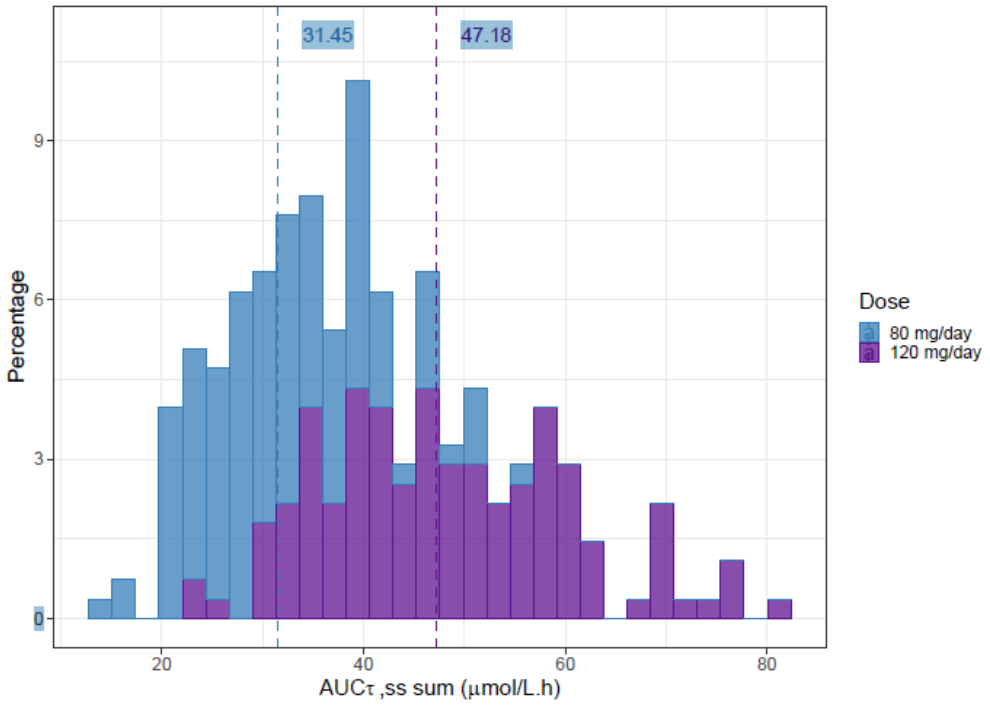


Figure 6: Histogram showing the distribution of predicted $AUC_{t,ss}$, for the participants with pk data in the combined alkaline phosphatase (ALP) and total bilirubin (TBIL) analysis data set receiving elafibranor.

ALP=alkaline phosphatase, AUCτ,ss sum=sum of the areas under the concentration-time curve during a dosing interval at steady state of elafibranor and GFT1007, PK=pharmacokinetics, TBIL=total bilirubin.

Data Source: REP-EMA-1-IPS-ELA-PMX-3, Figure S10

It is known that the $AUC_{\tau,ss\ sum}$ at half maximum effect ($AUC_{\tau,ss\ sum,50}$) is approximately 24 µmol*h/L for ALP and the saturation in the ALP response was observed for $AUC_{\tau,ss\ sum}$ of approximately more than 30 µmol*h/L. With **Figure 5** the 80 mg/day regimen showed a clear effect and improvement in the ALP and TBIL response compared to placebo. For TBIL only a minor drug effect is observed. The majority of individually-predicted $AUC_{\tau,ss\ sum}$ for the 80 mg regimen (around 60%) in the resampled distribution is in excess of the $AUC_{\tau,ss\ sum,50}$ (i.e. $AUC_{\tau,ss\ sum}$ at half maximum effect, ±24 µmol*h/L) for ALP.

However, from **Figure 6** it can be read that the median values of the $AUC_{\tau,ss\ sum}$ in the 80 and 120 mg/day treatment groups are 31 µmol*h/L and 47 µmol*h/L, respectively. Looking at the new predictions in **Figure 6** it seems like the higher exposure range (>60 µmol*h/L) includes participants on both 80 and 120 mg/day treatments (there appear to be some blue lines behind the purple boxes), suggesting the upper limits are similar for these two treatments. For the lower range, it is clearly visible a number of participants on the 80 mg/day treatment do not reach the $AUC_{\tau,ss\ sum,50}$ (of 24 µmol*h/L), let alone the threshold for saturation in ALP response (of 30 µmol*h/L). The latter seems to be the case for almost half of the subjects included in the 80 mg treatment group. This raises the question whether a dose of 120 mg/day would not have a larger benefit to the exposures in the entire population.

From the joint model, simulations were performed using the criteria defining the primary endpoint of Study 319-1. As can be seen in **Figure 5** for ALP at the median average exposure observed in the data, the typical exposure-response curve predicted similar change from baseline at Week 52 for 80 and 120 mg, whether the threshold was 15% (panel A) or 1.67xULN (panel B). Similarly, for TBIL, when the change from baseline at Week 52 was compared to the ULN threshold, similar efficacy was predicted from the model at 80 mg median exposure or 120 mg median exposure at steady state. No beneficial effect of a 120 mg regimen could be seen from those simulations.

These findings support the choice of elafibranor 80 mg as the (lowest) efficacious dose for participants with PBC from both studied doses. However, given the data and models the lowest efficacious dose and the full dose-response relationship cannot be established from the model nor from the data.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

Elafibranor and GFT1007 were analysed in plasma and urine using validated LC-MS/MS assays. Overall, full validations were carried out according to the "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217 /2009 Rev.1 Corr.2) in force when the trials and relevant PK analyses took place. The analytical methods were sufficiently validated.

In study 118-14 (hepatic impairment study), an analytical method was used (version 13 of method PKH/MOA/160) which was found in a cross-validation study (KIN5-015) to underestimate elafibranor concentrations. However, two groups were compared to each other, and the same assay was used for all samples. Also, the concentrations of GFT1007 were not affected by this issue and the results of GFT1007 indicate towards the same conclusion as the results of elafibranor, i.e. no significant effect on hepatic function except for the effect of unbound concentrations on severe hepatic impairment. Moreover, the confidence intervals in this study were quite wide, also for GFT1007 (i.e. where this method effect was not present), indicating that also without this method effect, there is some variability. It is therefore not expected that this effect will change the conclusion significantly. Another study in which this method was used, 218-1 (a phase II paediatric study in NASH patients) is not relevant for the current indication.

Stability of elafibranor in plasma at -20 °C was limited. Long-term stability at this temperature was established up to maximally 139 days. In one study elafibranor was found stable at -20 °C up to 6 months, but in another study, elafibranor was not stable after a comparable period of time (172 days). Elafibranor was stable in plasma at -80 °C for up to 456 days. GFT1007 was stable for 18 months at -20 °C and for 386 days at -80 °C. In the pivotal studies, plasma samples were stored at -80 °C. Both elafibranor and GFT1007 were not very stable in urine. Therefore, concentrations in urine may be less reliable.

The mass-balance study 114-10 investigated the metabolic profile of a 120 mg dose of ^{14}C-elafibranor in 6 healthy males. Total radioactivity in plasma, whole blood, urine, faeces, and in expired air was determined by liquid scintillation. The total amount of administered radiocarbon was 1.63-1.81 MBq (44.1-48.8 µCi). The label position of ^{14}C was provided in the second round. The label position was adequate because the ^{14}C labelling is retained with any metabolic pathway.

Population-based pharmacokinetics modelling

Clarification of the PopPK model was requested on the inclusion of the bioanalytical methods as covariate effects since it waswas unclear how the deviating results originating from different bioanalytical method versions have been compensated for in the popPK model. The applicant clarified that method versions 11 to 14 all refer to the same assay as version 13 (used in studies 118-14 and 218-1, see above) and that versions 9 and 10 were not used for any clinical study analyses.

Overall, the PopPK analysis has been sufficiently described. Yet successful minimization of the PK models was not attained, and condition numbers associated with the final models are high and appeared to be sensitive to several external modifications. The overparameterization in these models might be beneficial in light of the generalization of the noisy dataset that was used. Based on the

standard GOF plots major model misspecifications were not evident. Minor model misspecifications were discussed by the modelling CRO.

In conclusion, the PopPK models are deemed fit for purpose to estimate global covariate effects and derive exposure metrics for sequential PK/PD analyses of elafibranor and GFT1007. The impact of the models is probably low as all the conclusions drawn from the models are supported by direct conclusions from clinical data. The current PopPK models are not considered suitable for future extrapolation purposes.

Bioavailability

Absolute bioavailability is unknown. Because of the low solubility, no study was performed with intravenous administration. Urinary excretion was 19% and faecal excretion 77%. Although it cannot be concluded with certainty which part of the amount excreted in faeces had been previously absorbed, a study in bile-duct cannulated rats (71% of radioactivity was recovered in bile in the first 24 h , see non clinical assessment) indicates that biliary excretion may be a major pathway. Also, in humans a peak is visible in the concentration-time profile around 4 h indicating some enterohepatic circulation. A high biliary excretion together with urinary excretion of 19% indicates that bioavailability may be high. This is supported by a high passive *in vitro* permeability. Although solubility actually was not extremely low and a study could have been performed with a tracer dose given IV, this issue will not be further pursued. The applicant provided sufficient information on the in-vitro solubility (low) and cell permeability of elafibranor for conditional BSC Class II or IV classification. However, whether Class II or IV is applicable cannot be determined, because high bioavailability cannot be verified *in vivo* (though permeability was high *in vitro*, but the study design of the permeability study did not comply completely with the recommendations in the ICH M9 Guideline).

Food effect

Although the food effect study 452 confirmed the significant impact on C_{max} for elafibranor (50% reduction under fed conditions) and to a lesser extent its active metabolite GFT1007 (30% reduction under fed conditions), the impact on the exposure (AUC_t and AUC_{inf}) of elafibranor was limited to 15% with no change to the overall exposure of GFT1007. Since food had no clinically relevant effect on AUC and the decrease in Cmax will not impact the overall safety profile (see section 5.2 of the SmPC), it is agreed that in section 4.2 of the SmPC no advice is given regarding administration with or without food. AAn decrease in Cmax (only for parent drug) under fed conditions is not expected to impact the overall safety profile, as absence of significant impact of food on AUC for both elafibranor and GFT1007 was confirmed and as exposure in terms of AUC could be considered a stronger driver (with respect to Cmax) for a drug intended for chronic administration (as elafibranor).

Elimination

The elimination half-life was 68 h for elafibranor and 15 h for GFT1007. The shorter half-life of GFT1007 is considered to be due to high first-pass metabolism of elafibranor in the enterocytes and slow elimination of elafibranor from the systemic circulation.

Special populations: renal impairment

The results submitted by the applicant regarding the effect of renal function on exposure to elafibranor and its active metabolite GFT1007 are not entirely consistent looking at both the clinical study results and the covariate analysis with the popPK model (only for GFT1007). The applicant was therefore requested to clarify the role of renal function on the exposure to elafibranor and its main metabolite to give correct guidance to physicians in the SmPC. The main excretion pathway for both elafibranor and GFT1007 is via the feces: 77.1% of the dose was recovered in the feces, primarily as elafibranor (56.7% of the administered dose) and its active metabolite GFT1007 (6.08% of the administered

dose). Study 118-13 conducted in renally impaired participants with end stage renal disease confirmed that renal function did not have an impact on either C_{max} or AUC_{∞} of elafibranor or GFT1007, based on both total and unbound levels of elafibranor and GFT1007. A similar outcome was seen in the elafibranor PK model wherein creatinine clearance was not found to be a significant covariate. However, creatinine clearance was found to be a significant covariate in the GFT1007 PK model. A slight overprediction could contribute to the extent of effect of creatinine clearance for the renally impaired patients shown in the forest plot. AAA decrease in renal function, in particular for patients with ESRD, is not expected to affect the PK of either elafibranor or GFT1007 in a clinically relevant manner. Overall, the collected evidence, both empirical and simulated, suggests that exposure to elafibranor and GFT1007 is not clinically different between patients with either impaired or normal renal function. Therefore, no dose recommendations or dose adjustments are necessary.

Special populations: Age

Study 119-16 was conducted to evaluate the PK of elafibranor 120 mg in healthy elderly and young adult volunteers. Up to 30 healthy participants were planned to be enrolled to have 12 participants who would complete the study in each arm. However, due to premature study discontinuation, a total of 21 participants were enrolled, with 11 elderly participants and 10 young participants. No statistically significant differences in the PK of elafibranor were observed in healthy elderly participants, 75 to 80 years of age (Study 119-16), compared to healthy young adult participants (18–45 years old). The drug exposure to GFT1007 was found to be higher in the elderly population. CL/F and Vd/F are similar between the two populations, so the reason for this increased exposure in elderly subjects is not clear.

The applicant was asked to discuss if the study is still powered to highlight differences in PK profile between elderly and young participants on the basis of the reduced sample size, discuss about plausible reasons leading to the increase in exposure in PBC elderly patients and possible clinical consequences of this increase. In addition, data from study 119-16 and data from the popPK report are not aligned, which was also requested to be discussed.

The applicant clarified that no formal sample size was estimated for Study 119-16 and that a reduced number of patients respect to that planned have been enrolled, due to the Covid-19 outbreak in 2019, leading to a premature end of the study. In addition, Study 119-16 was designed to be a pilot trial of limited size to evaluate if any sizeable differences in the PK profile of elafibranor and GFT1007 between older and younger subjects were observed. The applicant justified the results from study 119-16 and the popPK report are not aligned in terms of age effect elafibranor exposure; and in terms of difference in weight on GFT1007 exposures. For the latter, median weights of 68.2 vs 79.8 kg in elderly vs young subjects, respectively, were observed in study 119-16; whereas the popPK model is not strongly affected by differences in weight between groups, as the covariates are accounted for in the model. The justifications are plausible and considered to be acceptable, hence the issues raised with regards to age effects have been resolved.

Dose proportionality

The applicant acknowledges that there appears to be some differences in the conclusions with regard to dose linearity between some of the individual studies compared to the population PK (popPK) analysis. Different conclusions in some studies may be due to the limited number of subjects in these studies coupled with high inter-individual variability. However, the popPK analysis encompassing all PK data available showed that dose-proportionality has been sufficiently justified for dose levels beyond 50 mg.

Drug-drug interactions

In the *in vitro* drug-drug interaction studies, it was not discussed whether actual concentrations of the test compounds have been measured and /or whether non-specific binding may have occurred. In

most *in vitro* interaction studies, non-specific binding was not investigated. In one study, study IPS000980, recovery was determined. In this study, recovery was low in assays with vesicles, whereas recovery was high in cell-based assays. This indicates that elafibranor and GFT1007 did not bind significantly to the cells used. Therefore, it is plausible that, at least in the other cell-based experiments, the actual concentrations were high enough.

GFT1007 inhibited UGT1A6 *in vitro* (IC50 value of 1.53 µM is below the systemic cut-off value for GFT1007 of 2.66 µM). According to the applicant, there are not many UGT1A6 substrates with glucuronidation as major pathway. However, paracetamol is an UGT1A6 substrate (Drugbank online) which has glucuronidation as a major pathway. A publication was provided (Court et al, 2001), which showed that the contribution of UGT1A6 to the glucuronidation of paracetamol is low compared to UGT1A9 and that a clinically relevant impact of inhibition of UGT1A6 by GFT1007 on the glucuronidation of paracetamol can be considered unlikely. UGT1A6 is also involved in the elimination of endogenous serotonin. However, the applicant provided information showing that metabolism of serotonin by UGT1A6 is only a minor pathway. Serotonin is mainly metabolised by monoamine oxidase (MAO). Inhibition of UGT1A6 is therefore considered to have no clinically relevant impact on the elimination of serotonin.

In the study in which inhibition of P-gp and BCRP was investigated *in vitro* (study KIN1-025c), IC50 values may not be completely reliable due to solubility limitations. However, the effect on BCRP was also investigated *in vivo*. No increases were observed in the exposure to BCRP substrates simvastatin and atorvastatin. Therefore, no interaction is expected with BCRP substrates. Regarding P-gp, IC50 was > 300 µM for both elafibranor and GFT1007. Therefore, also for P-gp it is considered unlikely that the conclusion would be changed to a significant extent due to the solubility limitations.

Pharmacodynamics

Elafibranor acts as a dual peroxisome proliferator-activated receptor (PPAR)α/δ agonist, and its pharmacological activity is driven by both the parent drug and GFT1007. Pharmacology will be discussed under the clinical efficacy. Like for fibrates the, the rationale for evaluation of elafibranor in Primary Biliary Cholangitis is based on its pharmacological properties as a PPARα/δ agonist. Data from several studies showed that the use of fibrates results in a significant reduction in cholestatic parameters (serum ALP and GGT), transaminases, and IgM levels in PBC patients and that most of them sustained the biochemical response as long as they were on fibrates [Ali 2015].

A notable and consistent decrease from baseline at week 52 in total cholesterol was reported. The main contributors for those decreases were significant reductions in TGs and VLDL-C, and to a lesser extent reductions in LDL-C, while HDL-C remained stable.

Based on *in vitro* human ether-à-go-go related gene (hERG) assays, it was concluded that elafibranor should not affect cardiac repolarization *in vivo*. The clinical studies (especially part 1 of study 113-9) do not indicate an QT prolongation either.

<u>PD interactions</u>

Early research suggested that elafibranor and its metabolite GFT1007 might be able to promote secretion of GLP-1 from intestinal epithelial cells, potentially enhancing the antidiabetic efficacy of dipeptidyl -peptidaseIV- inhibitors like sitagliptin. Therefore, a PD interaction study (109-6) was performed to determine the PD effect of elafibranor on sitagliptin-enhanced GLP-1 response during a meal test. This was a placebocontrolled, -multipledose study in 30 healthy male participants (randomised 2:1 elafibranor:placebo). Elafibranor (or placebo) was given once daily for 15 days (Day 3 to Day 17) and sitagliptin was given as single dose on 2 occasions: once alone (Day 2), and once concomitantly with elafibranor (or placebo) (Day 17). The following treatments were given: Day 2,

100 mg sitagliptin; Day 3 through Day 16, 100 mg elafibranor or placebo once daily; and Day 17, 100 mg sitagliptin and, 1 hour later, 100 mg elafibranor or placebo.

Sitagliptin resulted in higher plasma GLP1 concentrations after a test meal compared to a test meal with no sitagliptin (Day 2 versus Day 1). The overall GLP1 response after sitagliptin was not affected by elafibranor (Day 17 versus Day 16). In addition, there was no difference between the elafibranor and placebo group on Days 16 and 17, indicating that elafibranor itself did not affect GLP1 production. A lack of PD interaction of elafibranor on the pharmacological effect of sitagliptin was demonstrated.

2.6.4. Conclusions on clinical pharmacology

The applicant submitted a comprehensive data package on clinical pharmacology. Elafibranor acts as a dual peroxisome proliferator-activated receptor (PPAR)α/δ agonist. Based on *in vitro* and *in vivo* studies, no clinically relevant drug-drug interaction is expected by co-administering elafibranor with any other medicinal products. No QT prolongation is to be expected as elafibranor does not affect the cardiac repolarisation *in vitro*.

With regard to hepatic impairment the total drug exposure of the parent and active metabolite was not significantly different between participants with normal hepatic function and hepatically impaired participants (Child Pugh A, B and C). No dose adjustment is therefore required for patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. However, the unbound fraction of elafibranor and GFT1007 increased by approximately 3-fold in the severe (Child Pugh C) hepatically impaired participants. Elafibranor is therefore not recommended for patients with severe hepatic impairment (Child-Pugh C) as mentioned in 4.2 and 5.2 of the SmPC.

The pharmacology of elafibranor in the clamed indication is considered sufficiently characterised.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

2.6.5.1.1. Study GFT505B 216-1

Phase II randomised, double-blind, placebo controlled, efficacy and safety study in patients with PBC and inadequate response to UDCA.

2.6.5.1.2. Diagnosis and Criteria for Inclusion:

The inclusion/exclusion criteria were designed to include individuals 18 to 75 years of age with PBC and inadequate response to UDCA. 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 anti-mitochondrial antibodies titres (>1:40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay or positive PBC-specific antinuclear antibodies)
- Liver biopsy consistent with PBC

Further patients should have ALP ≥1.67 x upper limit of normal (ULN) and Total bilirubin (TB) ≤2 x ULN by inclusion. To ensure inclusion of a relevant ratio of participants with substantial risk of long-term clinical outcomes or moderate disease stage, it was planned that approximately 10% of randomised participants would be moderately advanced per Rotterdam Criteria (TB >ULN or albumin

[ALB] <lower limit of normal) and approximately 20% would have a TB >0.6 x ULN (participants at risk of progression)

2.6.5.1.3. Sample size

Fifteen patients in each of the elafibranor arms and placebo arm would achieve greater than 80% power to detect a percentage decrease of 20% for each dose-placebo comparison, using an unequal-variance t-test with a two-sided significance level (alpha) of 0.05 and assuming a standard deviation in each elafibranor arm of 18 and 15 for placebo arm.

This study projected to randomise approximately 45 subjects to 3 treatment groups in a 1:1:1 ratio (elafibranor 80 mg, elafibranor 120 mg, or placebo).

2.6.5.1.4. Treatment

Elafibranor tablet 80 mg and 120 mg once daily

Placebo tablet

The expected per-protocol exposure to study drug was 84 days (12 weeks).

2.6.5.1.5. Randomisation

Eligible patients will be randomised in a 1:1:1 ratio to receive elafibranor 80 mg, elafibranor 120 mg, or placebo using centralized randomisation (IVRS/IWRS).

2.6.5.1.6. Blinding

During the study, the Investigator, patient, and study personnel were blinded to the treatment allocation. Both elafibranor and placebo tablets and packaging were indistinguishable. The randomisation code may be broken by the Investigator when urgent action was required for the clinical management of the patient.

2.6.5.1.7. Primary objective

To evaluate the efficacy of elafibranor 80 and 120 mg with respect to relative change at week 12 from baseline in serum ALP levels compared to placebo. Each intervention arm is tested against placebo arm.

2.6.5.1.8. Estimand for the primary objective

No estimand was described.

Analysis sets:

The Enrolled Set includes all subjects who sign informed consent.

The Safety Set (SS) includes all randomised subjects who were administered at least one dose of study medication.

The Intent-to-Treat (ITT) population includes all randomised subjects.

The modified ITT (mITT) include all randomised patients receiving at least one study drug dose with available baseline value and at least one post baseline value for the primary endpoint.

The per-protocol Set (PPS) includes all subjects from the mITT population who are compliant with the study protocol without any major protocol deviations.

2.6.5.1.9. Secondary and tertiary objective

To assess the following endpoints at Visit 5 (Week 12):

- the response to treatment based on composite endpoints:
- ALP < 1.67 × upper limit of normal (ULN) and total bilirubin within normal limit and > 15% decrease in ALP
- ALP < 2 × ULN and total bilirubin within normal limit and > 40% decrease in ALP
- response according to Paris I, Paris II, Toronto I, Toronto II, UK PBC risk score
- ALP response rates of at least 10%, 20%, and 40% decreases
- the response to treatment on normalization of ALP
- the response to treatment on normalization of bilirubin
- the response to treatment on normalization of albumin
- the change from baseline in ALT, AST, GGT, 5'nucleotidase, total bilirubin, conjugated bilirubin, and albumin
- the change from baseline in lipid parameters
- the change from baseline in bile acids
- the change from baseline in C4, FGF19
- the change from baseline in IgM
- the change from baseline in inflammatory and liver fibrosis markers
- the change from baseline in pruritus (through 5D-itch scale and visual analogue score [VAS])
- the change from baseline in quality of life (using PBC 40 questionnaire)

The **primary endpoint** of the study is relative change from baseline in serum ALP levels comparing each elafibranor dose group to placebo at week 12 (Visit 5 or EOT value, must be last post baseline value under treatment).

Relative change in ALP is calculated by: [(Week 12 value – Baseline Value) / Baseline value)] x 100.

Primary efficacy analysis:

The relative change in ALP from baseline is analysed with a nonparametric randomization-based Analysis of Covariance method (LaVange et al, 2005). This methodology uses weighted least squares on the treatment differences of outcome and covariate means.

Each dose-placebo comparison is performed independently, not accounting for multiplicity.

Sensitivity analysis: A supportive analysis of elafibranor's effect on ALP changes is conducted based on an analysis of covariance (ANCOVA) model, with relative change in ALP from baseline as the response variable and with the treatment arm and baseline ALP level as explanatory variables.

2.6.5.1.10. Baseline characteristics and demography

Disposition of Subjects

A total of 68 subjects were screened, and 45 subjects were randomised (**Table 6**). Twenty-three subjects were screen failures. The most common reason for screen failure was that the eligibility criteria were not met. Overall, 45 subjects comprised the ITT set, with 15 subjects randomised to each of the 3 treatment groups.

Forty-four subjects completed the 12-week treatment period (up through Visit 5), and 1 subject discontinued from study during the 12-week treatment period; the subject was enrolled in the elafibranor 120 mg treatment group and was discontinued from the study due to SAEs. Twenty-three subjects completed the study up through the 12-week treatment period and the EOS Visit (16 to 30 days after Visit 5). The remaining 21 subjects completed the study under protocol version 2.0, which did not include an EOS Visit.

Table 6: Subject Disposition – Screening and Randomization (Enrolled Set)

	Overall N = 68 n (%)
Subjects eligible	68 (100.0)
Screen failure	23 (33.8)
Subject withdrew consent	3 (4.4)
Eligibility criteria not met	19 (27.9)
Other	1 (1.5)
Randomised	45 (66.2)
Dosed with study drug	45 (66.2)

Note: Presented frequencies and the denominator used for percentages are based on subjects in the Enrolled Set.

Table 7: Subject Disposition (Intent-to-Treat Set)

	Elafibranor 80 mg N = 15 n (%)	**Elafibranor 120 mg N = 15 n (%)**	**Placebo N = 15 n (%)**	**Overall N = 45 n (%)**
Completed the 12-week treatment period	15 (100.0)	14 (93.3)	15 (100.0)	44 (97.8)
Discontinued from the study in the 12-week treatment period	0	1 (6.7)	0	1 (2.2)
Adverse event	0	1 (6.7)	0	1 (2.2)
Completed the study[a]	8 (53.3)	7 (46.7)	8 (53.3)	23 (51.1)

Abbreviations: EOS = end-of-study

Note: Presented frequencies and the denominator used for percentages were based on subjects in the ITT set and treatment assigned.

a Subjects are defined as having "completed the study" if they have completed the treatment period up to Visit 5 (Week 12) and completed the EOS Visit (16 to 30 days after Visit 5). Twenty-one subjects completed the study under protocol version 2.0, which did not include an EOS Visit

Protocol Deviations

Of all subjects randomised in the study, 4 (8.9%) had at least 1 important protocol deviation. The number of subjects with important protocol deviations was similar across treatment groups. The most common type of important protocol deviation was use of concomitant medications (2), followed by

enrollment criteria (1) and other (1; unblinding occurrence). A total of 3 subjects (1 subject in the elafibranor 80 mg treatment group, 1 subject in the elafibranor 120 mg treatment group, and 1 subject in the placebo treatment group) were excluded from the PPS for important protocol deviations that may have affected the efficacy analysis.

Demographic and Other Baseline Characteristics

A summary of the demographic data and other baseline characteristics for the ITT set is provided in **Table 8**. Overall, the mean age at study entry was 59.1 years, with a minimum of 40 and a maximum of 74 years. Gender was disproportionate, with 95.6% females. The majority of subjects were white (97.8%) and not Hispanic or Latino (77.8%). The mean BMI at baseline was 26.9 kg/m^2 (minimum 19.1 kg/m^2, maximum 39.7 kg/m^2). Among female subjects, 11.1% were of childbearing potential; the remaining female subjects were post- menopausal (78.9%) or surgically sterile (21.1%). The 3 treatment groups had similar demographic and baseline characteristics, which were representative of the clinical PBC population.

Table 8: Subject Demographic and Baseline Characteristics (Intent-to-Treat Set)

Variable **Statistic/Response**	**Elafibranor 80 mg** **N = 15**	**Elafibranor 120 mg** **N = 15**	**Placebo** **N = 15**	**Overall** **N = 45**
Age at study entry (years)				
Mean (SD)	56.5 (8.7)	60.4 (6.9)	60.5 (8.6)	59.1 (8.2)
Gender, n (%)				
Male	1 (6.7)	0	1 (6.7)	2 (4.4)
Female	14 (93.3)	15 (100.0)	14 (93.3)	43 (95.6)
Race, n (%)				
Black or African American	0	0	1 (6.7)	1 (2.2)
White	15 (100.0)	15 (100.0)	14 (93.3)	44 (97.8)
Ethnicity, n (%)				
Hispanic or Latino	3 (20.0)	2 (13.3)	5 (33.3)	10 (22.2)
Not Hispanic or Latino	12 (80.0)	13 (86.7)	10 (66.7)	35 (77.8)
Height[a] (cm)				
Mean (SD)	160.2 (7.8)	164.5 (5.4)	164.3 (7.4)	163.0 (7.1)
Weight[a] (kg)				
Mean (SD)	70.6 (12.3)	76.8 (18.7)	68.5 (14.4)	72.0 (15.4)
BMI[a] (kg/m^2)				
Mean (SD)	27.4 (3.8)	28.2 (5.6)	25.2 (3.5)	26.9 (4.5)

Abbreviations: BMI = body mass index; bpm = beats per minute; ITT = intent-to-treat; max = maximum; min = minimum; N/A = not applicable; SD = standard deviation.

Note: Presented frequencies and the denominator used for percentages are based on subjects in the ITT set and actual treatment received.

a At baseline.

b N/A for male subjects only.

Medical History and Concomitant Diseases

Overall, a total of 60.0% of subjects in the ITT set reported previous medical histories. Overall, the most commonly reported previous medical history by SOC (≥ 10% overall) were surgical and medical procedures (37.8%), gastrointestinal disorders (15.6%), neoplasms benign, malignant and unspecified (including cysts and polyps) (13.3%), and investigations (11.1%). Overall, the most commonly reported previous medical histories by PT were cholecystectomy (13.3%), hysterectomy (11.1%), biopsy liver (6.7%), breast cancer (6.7%), and female sterilization (6.7%).

Overall, a total of 7 (15.6%) subjects (3, 1, and 3 subjects in the elafibranor 80 mg, elafibranor 120 mg, and placebo groups, respectively) in the ITT set reported taking previous medications. All previous medications (lisinopril, paracetamol, chlorphenamine maleate, rifampicin, ibandronic acid, carisoprodol, phenylephine hydrochloride, vitex agnus-castus, and cholecalciferol) were reported by 1 subject each.

Hundred percent (100%) of subjects in the ITT set received a concomitant medication. Overall, the most commonly received concomitant medications by generic term were UDCA (100%), paracetamol (22.2%), colecalciferol (20.0%), ibuprofen (13.3%), lekovit CA (calcium with vitamin D) (13.3%), and levothyroxine (13.3%). The mean (range) dose of UDCA medication at the SV was 1000.0 (300 to 1500) mg.

2.6.5.1.11. Efficacy results:

Both elafibranor 80 mg and elafibranor 120 mg demonstrated a significant decrease ($p < 0.001$) in the primary efficacy criteria, the ALP relative change from baseline to Week 12, leading to highly significant treatment effect vs placebo when an analysis was conducted using a non-parametric randomisation-based ANCOVA with baseline ALP as covariate on the mITT set (see **Table 9, Figure 7**). The treatment effect estimate was -52.0% (95% CI [-62.5; -41.5]) for the elafibranor 80 mg treatment group and -43.9% (95% CI [55.7; 32.1]) for the elafibranor 120 mg treatment group. The supportive ANCOVA analysis with baseline ALP as a covariate on the mITT set confirmed the results, as well as the non-parametric randomisation-based ANCOVA on the PPS. There was no apparent difference in the magnitude of improvement between the 2 elafibranor doses suggesting a plateau of the dose-exposure-response. The effect was observed from the first visit following baseline (Visit 2 [Week 2]) and was maintained and reinforced up to the end of the active treatment period.

Table 9: Relative Change from baseline in serum alkaline phosphatase at week 12 –primary efficacy endpoint – primary and supportive analyses (modified intent-to-treat set)

	Statistic	**Elafibranor 80 mg N = 15**	**Elafibranor 120 mg N = 14**	**Placebo N = 15**
Baseline	Mean ± SD	350.6 ± 152.1	263.8 ± 142.8	296.2 ± 115.5
	Median	321.0	210.0	246.0
Week 12 (Visit 5 or EOT value)	Mean ± SD	180.7 ± 95.7	152.4 ± 76.3	309.7 ± 142.8
	Median	161.0	122.0	262.0

Relative change from baseline to Week 12 (%)	Mean ± SD	-48.3 ± 14.8	-40.6 ± 17.4	3.2 ± 14.8
	Median	-50.6	-41.4	1.4
Primary analysis - Non-parametric randomization-based ANCOVA with baseline ALP as covariate				
Treatment effect (vs placebo)[a]	Estimate	-52.0	-43.9	-
	95% CI	[-62.5 ; -41.5]	[-55.7 ; -32.1]	-
	p-value	< 0.001	< 0.001	-
Supportive Analysis – ANCOVA with baseline ALP as a covariate				
Treatment effect (vs placebo)[b]	Estimate	-51.4	-43.9	-
	95% CI	[-63.3 ; -39.5]	[-55.8 ; -31.9]	-
	p-value	< 0.001	< 0.001	-
Interaction: Baseline*trt	p-value	0.528		

Abbreviations: ALP = alkaline phosphatase; ANCOVA = analysis of covariance; CI = confidence interval; EOT = end-of-treatment; SD = standard deviation; trt = treatment.

[a] Non-parametric randomization-based ANCOVA with baseline ALP as a covariate. p-values were computed under the null hypothesis (based on re-randomizations of the population) while estimates and CIs were computed under the alternative hypothesis (based on repeated random sampling).

[b] ANCOVA with baseline ALP as covariate

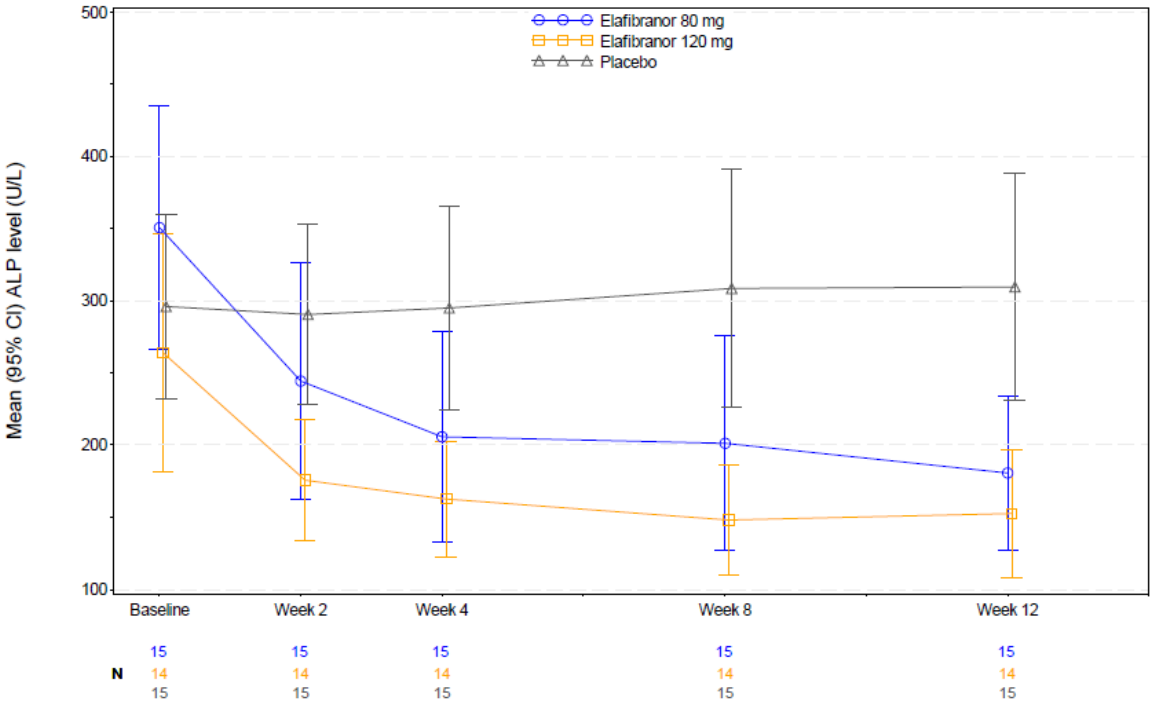


Figure 7: Mean alkaline phosphatase values from baseline through week 12 by treatment group (modified intent-to-treat set)

Both elafibranor 80 mg and elafibranor 120 mg demonstrated a statistically significant decrease ($p < 0.001$) in the absolute change from baseline in serum ALP at Week 12, leading to statistically significant treatment effect vs placebo, -164.4 U/L (95% CI [-212.0; -116.8]) for elafibranor 80 mg treatment group and -136.2 U/L (95% CI [-184.2; -88.3]) for the elafibranor 120 mg treatment group.

The percentage of subjects who achieved normalisation of ALP at Week 12 was higher in the elafibranor treatment groups: 2 subjects (13.3%) in the elafibranor 80 mg treatment group, 3 subjects (21.4%) in the elafibranor 120 mg treatment group, and no subjects (0%) in the placebo arm. In addition, a 40% reduction in ALP from baseline to Week 12 was seen in 86.7%, 57.1%, and 0% of subjects in the elafibranor 80 mg, elafibranor 120 mg, and placebo treatment groups, respectively; elafibranor 80 mg and 120 mg treatment groups had a statistically significantly greater proportion of responders compared to placebo ($p < 0.001$). These analyses support the results obtained on the primary endpoint.

The response rate to treatment based on the composite endpoint "ALP < 1.67 × ULN, total BIL within normal limits, and > 15% ALP reduction" from baseline to Week 12 was statistically significantly higher in the elafibranor 80 mg treatment group (66.7%, $p = 0.002$) and the elafibranor 120 mg treatment group (78.6%, $p < 0.001$) compared to placebo (6.7%). The response rate to treatment based on composite endpoint "ALP < 2 × ULN, total BIL within normal limits, and > 40% ALP reduction" from baseline to Week 12 was statistically significantly higher in the elafibranor 80 mg treatment group (73.3%, $p < 0.001$) and the elafibranor 120 mg treatment group (42.9%, $p = 0.006$) compared to placebo (0.0%).

The anticholestatic effect of elafibranor was confirmed by important reductions in mean GGT levels from baseline to Week 12 in the elafibranor treatment groups: -91.5 U/L mean absolute change and -37.1% mean relative change for the elafibranor 80 mg treatment group, -61.9 U/L mean absolute change and -40.0% mean relative change for the elafibranor 120 mg treatment group. Gamma-glutamyl transferase values barely changed in the placebo group (0.6 U/L for mean absolute change and 0.2% for mean relative change), leading to a treatment effect estimate (on relative change) vs placebo of -38.6% ($p = 0.001$) and -39.9% ($p = 0.002$) for the elafibranor 80 mg and the elafibranor 120 mg treatment groups, respectively. The effect was observed from the first visit following baseline (Visit 2 [Week 2]) and was maintained and reinforced up to the end of the active treatment period.

A sharp decrease in the absolute change of 5'nucleotidase, a specific marker of cholestasis, was also observed with elafibranor, leading to a treatment effect estimate (on relative change from baseline to Week 12) vs placebo 39.9% ($p = 0.002$) and -23.6% ($p = 0.178$) for the elafibranor 80 mg and the elafibranor 120 mg treatment groups, respectively.

Albumin levels, which were within the normal range at baseline for all but one subject, were statistically significantly increased (based on absolute change from baseline to Week 12) in both elafibranor treatment groups ($p \leq 0.054$). Total BIL, which was within normal limit at baseline in all but 1 subject, did not significantly change (based on absolute and relative change from baseline to Week 12 and response to treatment on normalization) when compared to placebo. Alanine aminotransferase and AST values did not significantly change (based on absolute and relative change from baseline to Week 12) when compared to placebo.

A clinically significant reduction in IgM (based on absolute change from baseline to Week 12) was observed in both elafibranor treatment groups ($p \leq 0.024$) whereas IgM remained relatively stable in the placebo treatment group ($p \leq 0.024$ for the elafibranor vs placebo group comparisons).

A significant anti-inflammatory effect was observed with an absolute reduction from baseline to Week 12 in haptoglobin values in both elafibranor treatment groups whereas they remained relatively stable in the placebo arm ($p \leq 0.031$ for the elafibranor vs placebo treatment group comparisons). Fibrinogen

levels were also reduced from baseline to Week 12 in both elafibranor treatment groups while they remained relatively stable in the placebo group. C-reactive protein (CRP) levels were drastically reduced from baseline to Week 12 and even normalized in both elafibranor treatment groups whereas they remained stable in the placebo group.

Serum levels of C4, a marker of bile acid synthesis, were elevated at baseline in all treatment groups; at Week 12 C4 levels were reduced in both elafibranor treatment groups whereas at Week 12 C4 levels increased in the placebo group. Fibroblast growth factor 19 values did not significantly change from baseline to Week 12 when compared to placebo.

Triglyceride levels at baseline were normal or slightly elevated (mean 1.2 mmol/L in both elafibranor treatment groups and 1.3 mmol/L in the placebo group). At Week 12, triglyceride levels were reduced with elafibranor treatment (mean change ± standard deviation [SD] of 0.2 ± 0.3 mmol/L, 0.3 ± 0.2 mmol/L in elafibranor 80 mg and 120 mg treatment groups, respectively); they remained stable in the placebo treatment group (mean change ± SD of 0.0 ± 0.4 mmol/L). Similarly, reductions on total and low-density lipoprotein cholesterol (LDL-C) from baseline to Week 12 were observed with elafibranor 80 mg and 120 mg treatment whereas they remained stable with placebo.

There was no significant decrease in high-density lipoprotein cholesterol (HDL-C) levels.

2.6.5.2. Main study

Study 319-1

A double-blind, randomised, placebo-controlled study and open label long term extension to evaluate the efficacy and safety of elafibranor 80 mg in patients with primary biliary cholangitis with inadequate response or intolerance to ursodeoxycholic acid

Methods

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 consists of a 2- to 12-week screening period, a 52- to 104-week DB period, followed by a 4- to 5-year LTE period, and a 4-week safety follow-up period after the last dose of study treatment. When applicable, participants continue their pre-study dose of UDCA throughout the study participation (**Figure 8**). The study design included a 52-week DB period (referred to as the common DB period) that was completed by all participants, followed by a variable DB period where participants continued to receive elafibranor or placebo until the last participant completed their Week 52 visit or the participant received 104 weeks of treatment, whichever came first.

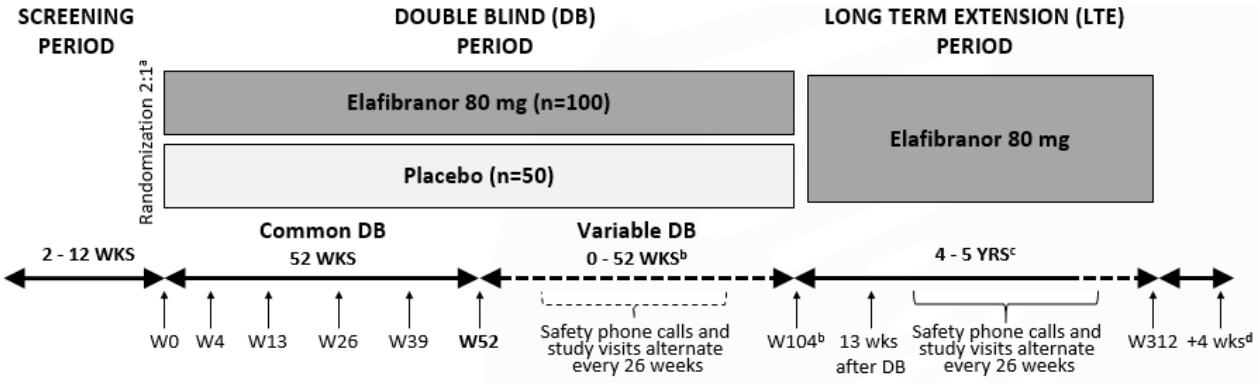


Figure 8: Study 319-1 design

DB=double-blind; LTE=long-term extension; UDCA= ursodeoxycholic acid; W=visit week; WKS=Weeks; YRS=years Data source: Study 316-1 Figure 1

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 (Week 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 participant'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.

Study Participants

Main key inclusion/exclusion criteria for participant eligibility were as follows:

- Males or females, 18 to 75 years of age, at screening visit 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 1)
    - Positive anti-mitochondrial antibodies titres (>1:40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay or positive PBC-specific antinuclear antibodies)
    - Liver biopsy consistent with PBC
- ALP ≥1.67 x upper limit of normal (ULN)
- Total bilirubin (TB) ≤2 x ULN
- To ensure inclusion of a relevant ratio of participants with substantial risk of long-term clinical outcomes or moderate disease stage, it was planned that approximately 10% of randomised participants would be moderately advanced per Rotterdam Criteria (TB >ULN or albumin [ALB] <lower limit of normal) and approximately 20% would have a TB >0.6 x ULN (participants at risk of progression)
- 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 (per country standard-of-care dosing)

Treatments

Participants were receiving elafibranor one 80 mg oral tablet once daily. Placebo tablets to match elafibranor 80 mg were provided.

The total duration of study participation is up to 6 years, or 328 weeks (2 to 12 weeks for the screening period, 52 to 104 weeks for the DB period, 208 to 260 weeks for the LTE period, and 4

weeks for safety follow-up). The total treatment period for each participant is expected to last 312 weeks, with a variable number of weeks in the DB period and in the LTE period depending on when the participant's last visit in the DB period occurred.

Rescue therapies to alleviate the pruritis (such as OCA) were allowed

Objectives

The primary objective of the double-blind (DB) period of the study was to evaluate the effect of elafibranor (80 mg/day) on cholestasis as defined by the primary endpoint over 52 weeks of treatment compared to placebo.

The key secondary objectives of the DB period of the study were to evaluate the effect of elafibranor (80 mg/day) over 52 weeks of treatment compared to placebo on:

- Normalisation of alkaline phosphatase (ALP)
- Pruritus based on change from baseline through Week 52 in primary biliary cholangitis (PBC) Worst Itch numeric rating scale (NRS) score in patients with baseline PBC Worst Itch NRS score ≥4
- Pruritus based on change from baseline through Week 24 in PBC Worst Itch NRS score in patients with baseline PBC Worst Itch NRS score ≥4

Other secondary endpoint is: Hepatobiliary injury and liver function markers, inflammation and hepatic fibrosis, lipid parameters, bile acids, pruritus PRO's, patient-reported fatigue, patient-reported sleep, patient-reported health-related quality of life, health utility, bone markers and bone density and safety and tolerability. To determine the pharmacokinetic (PK) parameters of elafibranor and its active metabolite GFT1007, at steady state following daily oral administration at 80 mg in participants with PBC

Explorative endpoints are constitute a biobank for discovery and validation of biomarkers associated with PBC, assist the interpretation of efficacy and safety results of elafibranor, to explore the correlation of fibrosis scores with non-invasive markers of fibrosis (liver stiffness, enhanced liver fibrosis [ELF] test and N-terminal type III collagen pro-peptide [Pro-C3]).

Outcomes/endpoints

The primary efficacy endpoint of the study was response to treatment at Week 52 defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%.

Key secondary endpoints included the following:

- Response to treatment based on ALP normalisation at Week 52
- Change in pruritus from baseline through Week 52 based on PBC Worst Itch NRS in participants with baseline PBC Worst Itch NRS score ≥4
- Change in pruritus from baseline through Week 24 based on PBC Worst Itch NRS in participants with baseline PBC Worst Itch NRS score ≥4

Sample size

One hundred and fifty patients (100 elafibranor vs 50 placebo) allow to achieve at least 90% power to demonstrate a statistically significant between group difference of 35% (47% in elafibranor group vs 12% in placebo group) in the response rate at week 52 of the primary efficacy endpoint with a two-sided alpha of 0.05 and using an exact Fisher test.

Randomisation and Blinding (masking)

Patients are randomised in a 2:1 ratio to receive elafibranor 80 mg or Placebo, using a central randomisation system. The randomisation was stratified by two factors:

1. ALP > 3x ULN or Total bilirubin > ULN: Yes/No, and

2. PBC Worst Itch NRS averaged - over the 14 days preceding randomization - ≥ 4:Yes/No.

The investigator, patient, and study personnel were blinded to the treatment. Both elafibranor and placebo tablets and packaging are indistinguishable. Values of ALP, GGT and 5'NT remained blinded for the Investigator and for the patient up to the DB database lock. Rescue therapy for PBC and Pruritus was identified during the Blind Data Review Meetings (BDRM).

Statistical methods

Intent-to-treat (ITT) Analysis Set: All randomised patients.

Pruritus ITT Analysis Set: All patients from the ITT analysis set with baseline PBC Worst Itch NRS score ≥4.

Per Protocol (PP) Analysis Set: All patients from the ITT population without any major protocol deviation or event affecting the primary efficacy endpoint.

Pruritus PP Analysis Set: All patients from the Pruritus ITT analysis set without any major protocol deviation or event affecting the primary efficacy endpoint and/or the second and third key secondary endpoint.

Primary efficacy endpoint and primary efficacy analysis

Primary efficacy composite endpoint: Cholestasis response at Week 52 defined as ALP <1.67 x ULN and TB ≤ULN and ALP decrease ≥15%. Patients who stopped prematurely the study treatment (ICE-1) or used rescue therapy for PBC (ICE-2) prior to week 52 assessment are considered as non-responders. Missing data at week 52 (i.e. visit 6) for patients without ICE are replaced by the closest non-missing assessment from the DB treatment period before or after the theoretical visit 6 date 6.

Primary efficacy analysis: The primary efficacy analysis is based on the exact Cochran-Mantel-Haensel (CMH) test stratified by the randomization factors, where the estimated risk difference is a stratum-adjusted risk difference with CMH weights and using the Newcombe method for the calculation of the 95% CI. For consistency, the 95% CIs for the single proportions are based on the Wilson score method. For estimation of the odds ratio and the corresponding 95% exact CI, the analysis is also based on the exact Cochran-Mantel-Haensel (CMH) test stratified by the randomization factors. The primary efficacy analysis is performed for the ITT set and based on the composite strategy where ICEs (study treatment discontinuation and use of rescue medication) are considered as non-response irrespective of the data after the intercurrent event.

Five ICEs considered of relevance for primary and secondary estimands have been outlined (treatment discontinuation, use of rescue therapy for PBC or pruritus, use of concomitant medication that increases or reduces pruritus).

The following supplemental analyses are performed:

1. Composite strategy with missing data as non-responders: The exact same composite strategy as for the main analysis, except that patients without ICE but missing data at week 52 are considered as non-responders using the ITT analysis set.

2. Hypothetical strategy: Two relevant multiple imputation methods (based on assigned treatment and based on placebo) of the primary endpoint are performed imputing outcomes

experienced after an ICE at Week 52 and using the ITT analysis set. The imputations of post ICE-1 or ICE-2 ALP and TB are based on patients completing the week 52 DB period and relevant baseline covariates.

Key secondary efficacy analyses

- First key secondary efficacy analysis: The same analyses as for the primary efficacy endpoint are performed, however the stratified Newcombe method was not estimable and was used unstratified.
- Second and third key secondary efficacy analysis: The analyses are performed on the change in pruritis from baseline through week 52 and week 24, respectively, using the Mixed Model Repeated Model (MMRM) method with treatment, 4-week period and treatment by 4-week period interaction as fixed and adjusting for baseline PBC Worst Itch NRS score and the stratification factor [ALP > 3x ULN or TB > ULN-(Yes/No)] as covariates. These analyses are performed for the pruritis ITT analysis set. PBC Worst Itch NRS scores for patients who stopped prematurely the study treatment (ICE-1) or took a rescue therapy for pruritus (ICE-3) prior to week 52 assessment will be considered as missing. For the key secondary endpoints, missing data at week 52 (i.e. visit 6) for patients without ICE will be replaced by the closest non-missing assessment from the DB treatment period for the main analysis.

Interim: No interim analysis is planned.

Multiplicity: The fixed-sequence testing approach was used to control the overall type I error rate at a two-sided 0.05 level.

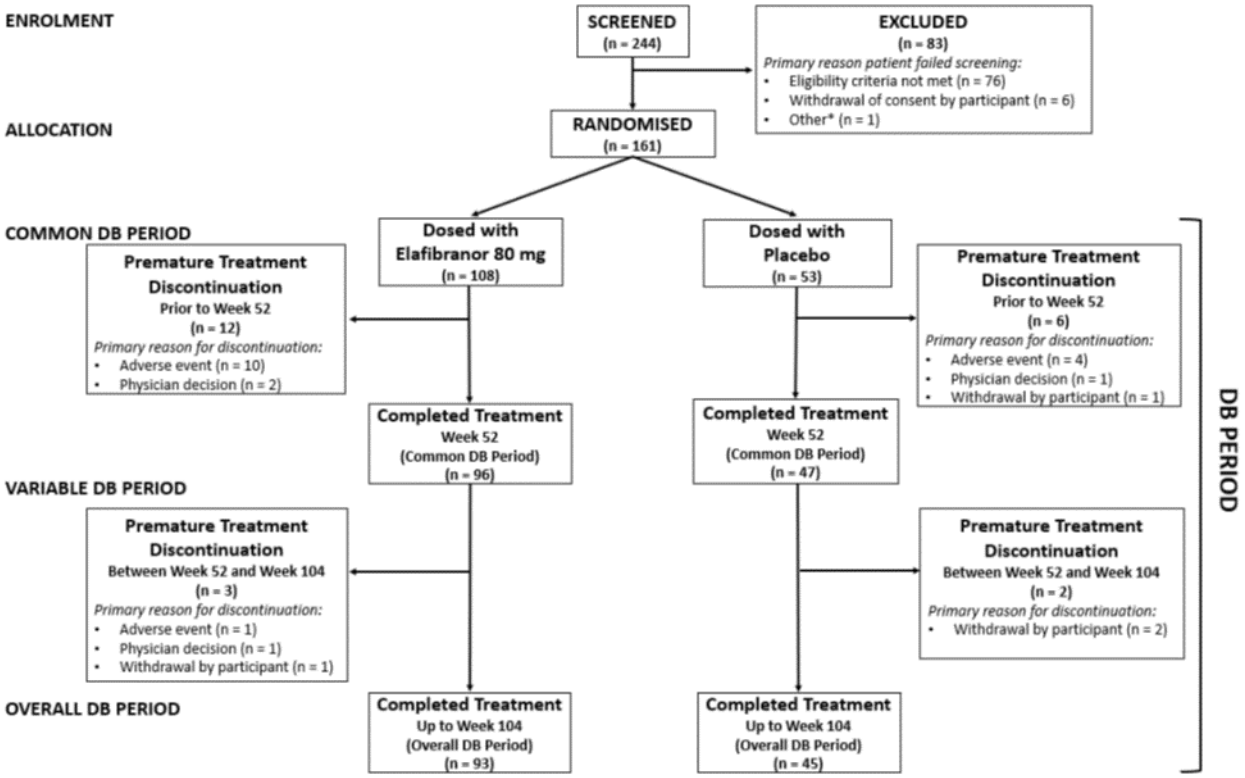
Changes following study unblinding in post-hoc analyses

After study unblinding, in case for binary response endpoints where the placebo response rate was observed to be zero, unstratified risk differences using the Newcombe method and corresponding 95% CIs were presented since the planned stratified Newcombe risk difference and corresponding 95% CIs were not estimable.

This was the case for the first key secondary endpoint. As an additional post-hoc sensitivity analysis, an exact 95% CI for the risk difference and exact Clopper-Pearson 95% CI for the response rates were also performed.

Results

Participant flow



DB=double-blind; ITT=intent-to-treat
*Other included the following reasons: out of time window, no suitable date before cohort closed.

Figure 9: Participant flow

Recruitment

Date of first enrolment: 24 September 2020

Date of last completed: 01 June 2023

The data cutoff for Study 319-1 was the 01 June 2023, which corresponded with the LPLV of the total (common + variable) DB period. At the time of the data cutoff, participants had variable treatment exposure; all participants who had not prematurely discontinued the study treatment, had at least 52 weeks and up to a maximum of 104 weeks of treatment exposure. The efficacy data presented in this report is primarily for the common DB period (i.e. until Week 52), while the safety data include all data available until the data cutoff (i.e. throughout the common and variable DB period up to a maximum of Week 104).

Conduct of the study

Table 10: Summary of substantial changes to study conduct

Section Number and Name	Description of Change
Amendment 1 (v2.0; 11 December 2020)	
Section 1.5 Rationale for Study Population	Added identifying patients with cirrhosis by elastography
Section 2.1.1.3 Secondary Objectives	Removed liver histology (both efficacy and safety criteria) for evaluating the effect of elafibranor as compared to placebo
Section 2.1.1.3 Secondary Objectives	Added pruritus PROs
Section 2.1.1.4 Exploratory Objectives	Added exploratory objectives related to histological assessment.
Section 2.2.1.2: Secondary endpoints	Added DEXA scanning assessments
	Removed progression to histological cirrhosis for non-cirrhotic patients at baseline from the onset of clinical outcomes endpoint composition
	Removed the change from baseline in the histological scores
	Added description of exploratory analysis for histological assessments
Section 2.2.1.3: Exploratory endpoints	Added exploratory endpoints associated with histological assessment
Section 3.5.1 Screening Period	Added information on timing of consent and timing of liver biopsy
Section 4.2 Exclusion Criteria	Updated Exclusion Criteria 9 for prohibited medications and previous exposure to OCA
	Updated Exclusion Criteria 10 related to exclusion of participants previously exposed to seladelpar
	Added Exclusion Criteria related to variability of AT or TB>40% for participants with AT or TB>ULN at SV1
	Replaced positive urine pregnancy test with positive serum pregnancy test
	Added hypersensitivity to the investigational product of any of its formulation excipients of elafibranor or placebo tablet
	Added mental instability or incompetence such that the validity of informed consent or ability to be compliant with the study is uncertain
Section 5.2.1 Permanent discontinuation of study drug/withdrawal from study	Added language to possible reasons that may lead to permanent early study drug discontinuation to include worsening or disease progression that would require initiation of any standard of care prohibited in the study
Section 6.1.3 Bone density by DEXA scanning	Added a row to the Study General Assessment Schedule table for hip and lumbar DEXA scanning
	Added information on use of DEXA scanning for bone density
Section 6.3.7 Clinical event committee	Updated language on the adjudication by the CEC
Section 6.4.1 Summary of safety data	Updated summary of safety data according to last IB update
Section 7.12.3. Permitted Medication Under Conditions	Updated permitted medication text that dose of current medication for chronic disease should remain unchanged as far as possible.
Section 9.4 Analysis Sets	Added exploratory (histological) analysis set definition
Section 12.3 Patient Information and Consent	Added separate consent forms for optional liver biopsy and pregnant partner data collection.

Section Number and Name	Description of Change
Amendment 2 (v3.0; 18 March 2022)	
Section 1.5 Rationale for Study Population; Section 3.1 Number of Patients; Section 3.5.2 DB period (Week 0 to max Week 104)	Edited text to remove the requirement for a minimum percentage of moderately advanced participants or participants at risk of progression, based on revised inclusion criteria#5.
Section 4.1 Inclusion criteria	Revised Inclusion Criteria #5 to adapt the requirement for a minimum % of noncirrhotic moderately advanced participants per Rotterdam Criteria and the minimum % of randomised participants at risk of progression (TB >0.6xULN), to approximately 10% and 20%, respectively.
Amendment 3 (v4.0; 20 September 2022)	
Throughout Protocol	The type I error rate was reset to 0.05 across the protocol.
Synopsis: Key Secondary Objectives and Synopsis: Criteria for evaluation – Key secondary endpoints	The key secondary objective and endpoint were modified to be evaluated in the subpopulation with moderate to severe pruritus at baseline (PBC Worst Itch NRS score ≥4). A third key secondary objective was added to assess pruritus at Week 24.
Synopsis: Criteria for evaluation – Other key secondary endpoints	An additional analysis to assess complete biochemical response was added.
	Analysis of worsening pruritus modified to through Week 52 and Week 24; analysis of responders in PBC Worst Itch NRS score modified to include clinically meaningful change and absolute score reductions of one point, two points or three points from baseline.
Synopsis – Statistical considerations – Analysis sets	Definition of population was clarified.
Synopsis – Statistical considerations – Efficacy analysis – Key secondary endpoints	Updated to include a short description of the statistical methodology applied to the change from baseline in PBC Worst Itch NRS score through week 24.
Synopsis – Statistical considerations – Efficacy analysis – Other secondary endpoints – Control of type I error rate	The type I error rate was reset to 0.05 across the protocol. A new key secondary objective was added.
Table 1: Study General Assessment Schedule; Table 4: Study Biological Assessment Schedule	LVDB anchored to V5 as opposed to V6 in order to allow switching of participants in a timely manner to the LTE with open-label treatment.
1.0 Introduction	Statement added to introduce Ipsen as a "partner" and to introduce a future change in sponsorship.
1.3.1 Phase 1 Program	Updated with the most recent data from Annual DSUR with cut-off date as of 31 July 2022.
1.5 Rationale for study population; 3.5.2 DB Period (Week 0 to Max Week 104)	The protocol aimed to include a relevant ratio of participants with substantial risk of long-term clinical outcome, or moderate disease stage. The criteria for identifying participants with more advanced disease were modified to not only include participants meeting Rotterdam criteria but also those with more advanced disease identified based on liver stiffness measurement by TE or histology.
2.2.1.2 Secondary endpoints, Key Secondary endpoints	Key secondary endpoints harmonized throughout the protocol with revised key secondary endpoints.
2.2.1.2 Secondary endpoints, Key Secondary endpoints – Other secondary endpoints	Added complete biochemical response as an additional analysis.
2.2.1.2 Secondary endpoints, Other Secondary endpoints	Analysis of worsening pruritus modified to through Week 52 and Week 24; analysis of responders in PBC Worst Itch NRS score modified to include clinically meaningful change and absolute score reductions of one point, two points or three points from baseline.
3.5.3 LTE period	Clarification on visit frequency in the open-label LTE.
6.1.1 Biological Assessments	Additional guidance provided to maintain the blind in the DB treatment phase.

Section Number and Name	Description of Change
8.1.2 Adverse Events of Special Interest (AESIs)	AESIs list updated to include hepatic injury and renal injury.
9.1 Estimands Considerations – Key secondary endpoints; 9.3.2 Secondary endpoints – Key secondary endpoints; 9.6.1 Key Secondary endpoints	Harmonisation of this section to reflect the revisions in key secondary endpoints.
9.6.3 Subgroups analyses	Addition of a subgroup analysis for participants with advanced disease, including cirrhotic participants defined by liver stiffness at baseline ≥16.9 kPa by TE (Yes/No) and/or cirrhosis on histology, and participants with advanced disease stage defined as liver stiffness at baseline >10 kPa by TE and/or bridging fibrosis or cirrhosis on histology.
9.8.3 Change in Pruritus	The updated SD of 2.3 in the pruritis power calculation is based on the blinded data analysis performed in July 2022.
12.3 Patient information and consent	Text edited to clarify the process for obtaining Informed Consent from the participants.
Amendment 4 (v5.0; 20 December 2022)	
Throughout protocol	Change made to show transfer of sponsorship from Genfit to Ipsen
8.3.2. Reporting an SAE or an AESI	Added / removed language in order to be consistent with Ipsen processes.
8.6.1. Pregnancy	Edited language to be consistent with Ipsen processes
10.1. Data protection	Added language surrounding data security breach to comply with Ipsen protocol template and procedure
12.3. Patient information and consent	Added language surrounding withdrawal of consent to comply with Ipsen protocol template

AESI=adverse event of special interest; AT=aminotransferase; CEC=clinical events committee; DB=double-blind; DEXA=dual-energy X-ray absorptiometry; DSUR=Development Safety Update Report; IB=Investigator's Brochure; LSM=liver stiffness measurement; LTE=long-term extension; LVDB=last visit double-blind; NRS=numeric rating scale; OCA=obeticholic acid; PBC=primary biliary cholangitis; PRO=patient reported outcome(s); SAE=serious treatment-emergent adverse event; SD=standard deviation; SV=screening visit; TB=total bilirubin; TE=transient elastography; ULN=upper limit of normal

- **Baseline data**

No meaningful imbalances in baseline disease-specific characteristics were observed between elafibranor and placebo treatment groups in the ITT Analysis Set (**Table 11**), except that median baseline values were greater in the elafibranor group than in the placebo group for ALP (296.5 U/L versus 254.0 U/L), GGT (161.5 U/L versus 146.0 U/L), and ALT (45.0 U/L versus 38.0 U/L).

The mean (SD) time since PBC diagnosis was 8.0 (6.2) years overall. The baseline mean (SD) ALP level was 321.9 (150.9) U/L. In total, 96.3% of participants had a baseline ALP >1.67 x ULN and 39.1% of participants had a baseline ALP >3 x ULN.

The baseline mean (SD) TB level was 9.61 (5.07) µmol/L, and the majority of participants (96.3%) had a baseline TB level ≤ULN. In total, 24.8% of participants had a TB> 0.6 x ULN at baseline, 3.7% had moderately advanced disease per Rotterdam criteria (TB >ULN or ALB <LLN), 10.4% had liver stiffness ≥16.9 kPa by TE and/or cirrhosis on histology, and 35.1% had liver stiffness >10 kPa by TE and/or bridging fibrosis or cirrhosis on histology. Overall, the mean (SD) LSM at baseline was 10.14 (8.16) kPa; 9.85 (7.83) in the elafibranor 80 mg group and 10.73 (8.87) in the placebo group. Levels of ALT, AST, and GGT were elevated at baseline, with baseline mean (SD) levels of 49.6 (32.6) U/L, 45.7 (27.2) U/L, and 215.5 (197.4) U/L, respectively. There were 66 (41.0%) participants with a PBC Worst Itch NRS score of ≥4; mean (SD) PBC Worst Itch NRS score was 3.26 (2.79). Similar results were observed for the PP Analysis Set.

Table 11: Baseline disease characteristics (ITT analysis set)

Characteristic	Elafibranor 80 mg (N=108)	Placebo (N=53)	Total (N=161)
Time (years) since PBC Diagnosis			
n (missing)	108 (0)	53 (0)	161 (0)
Mean (SD)	7.9 (5.9)	8.3 (6.8)	8.0 (6.2)
Min; max	1; 33	1; 28	1; 33
PBC Worst Itch NRS score			
n (missing)	108 (0)	53 (0)	161 (0)
Mean (SD)	3.29 (2.77)	3.20 (2.87)	3.26 (2.79)
Min; max	0.0; 9.8	0.0; 8.0	0.0; 9.8
ALP (U/L)			
n (missing)	108 (0)	53 (0)	161 (0)
Mean (SD)	321.3 (121.9)	323.1 (198.6)	321.9 (150.9)
Min; max	165; 833	151; 1398	151; 1398
TB (µmol/L)			
n (missing)	108 (0)	53 (0)	161 (0)
Mean (SD)	9.71 (5.13)	9.41 (4.99)	9.61 (5.07)
Min; max	3.0; 30.1	2.6; 29.0	2.6; 30.1
ALT (U/L)			
n (missing)	108 (0)	53 (0)	161 (0)
Mean (SD)	49.3 (29.4)	50.3 (38.7)	49.6 (32.6)
Min; max	13; 153	11; 188	11; 188
AST (U/L)			
n (missing)	108 (0)	53 (0)	161 (0)
Mean (SD)	45.0 (24.2)	47.2 (32.8)	45.7 (27.2)
Min; max	14; 138	14; 203	14; 203
GGT (U/L)			
n (missing)	108 (0)	53 (0)	161 (0)
Mean (SD)	213.3 (186.1)	220.0 (220.3)	215.5 (197.4)
Min; max	13; 1029	18; 891	13; 1029
ALB (g/L)			
n (missing)	108 (0)	53 (0)	161 (0)
Mean (SD)	43.4 (3.0)	44.6 (3.0)	43.8 (3.0)
Min; Max	36; 50	36; 51	36; 51
ALP >1.67 x ULN, n (%)			
n (missing)	108 (0)	53 (0)	161 (0)
Yes	105 (97.2)	50 (94.3)	155 (96.3)
No	3 (2.8)	3 (5.7)	6 (3.7)

TB >ULN or ALB <LLN, n (%)(Rotterdam criteria)			
n (missing)	108 (0)	53 (0)	161 (0)
Yes	4 (3.7)	2 (3.8)	6 (3.7)
No	104 (96.3)	51 (96.2)	155 (96.3)

ALB=albumin; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma rating scale; PBC=primary biliary cholangitis; Q1 = first quartile; Q3 third quartile; SD=standard deviation; TB=total bilirubin; ULN=upper limit of normal

- **Numbers analysed**

Of the 161 randomised participants (108 to elafibranor and 53 to placebo), 161 were treated and 148 completed the common DB period (Week 52) of the study.

- **Outcomes and estimation**

Primary Efficacy Endpoint: response to treatment based on cholestasis response

The primary endpoint of this study was the response to treatment based on cholestasis response at Week 52, defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%. Participants who prematurely discontinued the study treatment (ICE-1) or used rescue therapy for PBC (ICE-2) prior to Week 52 were considered as non-responders. Treatment comparison of the proportion of participants with cholestasis response at Week 52 using the exact CMH test stratified by the randomisation strata (ITT Analysis Set) is shown in **Table 12**.

At Week 52, the proportion of responders was 55/108 (50.9%) participants in the elafibranor group compared with 2/53 (3.8%) participants in the placebo group, resulting in a difference of 47.2% (95% CI: 32.0; 56.9) favouring the elafibranor group. The 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 were similar using the PP Analysis Set.

Table 12: Proportion of Patients 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)	37.6	
95% CI	[7.6; 302.2]	
p-value	<0.0001	

CI = confidence interval; CMH=Cochran-Mantel-Haenszel; ICE=intercurrent event; ITT=intent-to-treat
Data Source: Table 14.2.1.1.1

A sensitivity analysis, in addition to the exact CMH, was performed on the ITT Analysis Set, using an exact logistic regression model stratified by randomisation strata with treatment group as a factor. The sensitivity analysis confirmed the results for the Odds Ratio of the primary endpoint analysis. At Week 52, the OR (elafibranor versus placebo) was 33.0 ([95% CI: 7.6; 302.2]; p<0.0001).

Supplemental analyses (Composite strategy with missing data as non-responders, hypothetical strategy based on assigned treatment and hypothetical strategy based on placebo treatment) of the primary endpoint further support the robustness of the results reported for the primary endpoint.

Table 13: Cholestasis response at week 52 by randomisation strata

Cholestasis Response at Week 52	**Elafibranor 80 mg (N=108)**	**Placebo (N=53)**
Strata 1 (PBC Worst Itch NRS score ≥ 4) = Y, Strata 2 (ALP > 3x ULN or TB > ULN) = Y		
n	20	10
Proportion of responder	0.250	0.000
95% CI	[0.087; 0.491]	[0.000; 0.308]
Risk difference	**0.250**	
95% CI	**[-0.067; 0.491]**	
Strata 1 (PBC Worst Itch NRS score ≥ 4) = Y, Strata 2 (ALP > 3x ULN or TB > ULN) = N		
n	24	12
Proportion of responder	0.708	0.000
95% CI	[0.489; 0.874]	[0.000; 0.265]
Risk difference	**0.708**	-
95% CI	**[0.424; 0.874]**	-
Strata 1 (PBC Worst Itch NRS score ≥ 4) = N, Strata 2 (ALP > 3x ULN or TB > ULN) = Y		
n	23	11
Proportion of responder	0.261	0.000
95% CI	[0.102; 0.484]	[0.000; 0.285]
Risk difference	**0.261**	-
95% CI	**[-0.047; 0.484]**	-
Strata 1 (PBC Worst Itch NRS score ≥ 4) = N, Strata 2 (ALP > 3x ULN or TB > ULN) = N		
n	41	20
Proportion of responder	0.659	0.100
95% CI	[0.494; 0.799]	[0.012; 0.317]
Risk difference	**0.559**	-
95% CI	**[0.272; 0.730]**	-

ALP=alkaline phosphatase; CI=confidence interval' N=number of participants; n=number of participants with data; NRS=numerical rating scale; PBC=primary biliary cholangitis; TB=total bilirubin; ULN=upper limit of normal; vs=versus

First Key Secondary Endpoint: response to treatment based on alp normalisation

The first key secondary endpoint was the response to treatment based on ALP normalisation at Week 52, defined as ALP ≤1.0 x ULN (for males ULN was 129 U/L, for females ULN was 104 U/L). Participants who prematurely discontinued the study treatment (ICE-1) or used rescue therapy for PBC

(ICE-2) prior to the Week 52 assessment were considered as non-responders. Treatment comparison in the proportion of participants with ALP normalisation at Week 52 using the exact CMH test (ITT Analysis Set) is shown in **Table 14**.

The proportion of responders was greater in the elafibranor group (16/108 [14.8%] participants) than in the placebo group (0/53 [0.0%] participants), resulting in a difference of 14.8% (95% CI: 6.1; 22.7) favouring the elafibranor group. The OR was statistically significant in favour of elafibranor (OR=infinity [95% CI: 2.8; infinity]; p=0.0019). The results were similar using the PP Analysis Set.

Table 14: Proportion of participant with alp normalisation at week 52 – exact cmh test – first key secondary endpoint (ITT analysis set)

	Elafibranor 80 mg (N=108)	**Placebo (N=53)**
ALP normalisation at Week 52, n (%)		
n (missing)	108 (0)	53 (0)
Yes	16 (14.8)	0 (0.0)
No	92 (85.2)	53 (100.0)
No	80 (74.1)	47 (88.7)
No due to ICE	12 (11.1)	6 (11.3)
Proportion of responders	0.148	0
95% CI	[0.093; 0.227]	[0.000; 0.068]
Risk difference	0.148	
95% CI	[0.061; 0.227]	
Exact CMH		
Odds Ratio of response (elafibranor vs placebo)	Infinity	
95% CI	[2.8; Infinity]	
p-value	0.0019	

ALP=alkaline phosphatase; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; ICE=intercurrent event; ITT=intent-to-treat
Data Source: Table 14.2.2.1.1

The results for the Odds Ratio are confirmed by a sensitivity analysis using an exact logistic regression model with fixed effect for treatment group and randomisation strata as factor. Further robustness was demonstrated by several supplemental (Composite strategy with missing data as non-responders, Hypothetical strategy based on assigned treatment and Hypothetical strategy based on placebo treatment) analyses.

Other Key Secondary Endpoints: Change from Baseline in Pruritus

The second and third key secondary endpoints were the change in pruritus from baseline through Week 52 and Week 24, respectively, on PBC Worst Itch NRS score in participants with baseline PBC Worst Itch NRS score ≥4 (Pruritus ITT Analysis Set).

The mean (SD) baseline PBC Worst Itch NRS score in the Pruritus ITT population was 6.19 (1.50) for the elafibranor group and 6.25 (1.15) for the placebo group. The LS mean change through Week 52 in PBC worst itch NRS score (Pruritus ITT Analysis Set) was -1.930 in the elafibranor group and -1.146 in the placebo group, thus estimating greater reduction in pruritus in the elafibranor group. The LS means difference between elafibranor and placebo using the Pruritus ITT Analysis Set was -0.784 ([95% CI: -1.986; 0.418]; p=0.1970) (**Table 15**). Similar results were observed using the Pruritus PP Analysis Set and the ITT Analysis Set.

The LS mean change through Week 24 in PBC worst itch NRS score (Pruritus ITT Analysis Set) was -1.598 in the elafibranor group and -1.255 in the placebo group. The LS means difference between elafibranor and placebo was -0.343 ([95% CI: -1.489; 0.803]; p=0.5522) (**Table 15**). Similar results were observed using the Pruritus PP Analysis Set and the ITT Analysis Set.

Table 15: Change in Pruritus from baseline through week 52 and Week 24 – MMRM Test – Other Key Secondary Endpoints (Pruritus ITT Analysis Set)

PBC Worst Itch NRS Score Statistic	Elafibranor 80 mg (N=44)	Placebo (N=22)
Through Week 52		
Treatment effect through Week 52[a]		
LS means	-1.93	-1.15
95% CI	[-2.60; -1.26]	[-2.14; -0.15]
LS means difference with placebo	-0.78	--
95% CI	[-1.99; 0.42]	--
p-value	0.1970	--
Through Week 24		
Treatment effect through Week 24[b]		
LS means	-1.60	-1.26
95% CI	[-2.25; -0.95]	[-2.20; -0.31]
LS means difference with placebo	-0.34	--
95% CI	[-1.49; 0.80]	--

CI=confidence interval; ITT=intent-to-treat; LS=least squares; MMRM=mixed model for repeated measures; NRS=numeric rating scale; PBC=primary biliary cholangitis
Data Source: Table 14.2.3.1.1.1 and Table 14.2.4.1.1
a Treatment effect through Week 52 is the average of NRS changes from baseline for the six 4-week periods.
b Treatment effect through Week 24 is the average of NRS changes from baseline for the 13 4-week periods.

Various analysis using a varying combination of the ALP, TB and albumin further support the effects seen on the biomarkers of the liver function as seen in the primary and key secondary endpoint.

The UK-PBC Score and GLOBE Score are used to get some feeling of the transplantation-free survival at 5, 10, and 15 years. At Week 52, the median (IQR) change from baseline in the UK-PBC score was -0.29 (-0.60; 0.06) for participants on elafibranor and 0.09 (-0.32; 0.42) for placebo. At Week 52, the 5-, 10-, and 15-year survival rates increased from 99.19%, 97.32%, and 95.07% at baseline to 99.46%, 98.19%, and 96.65% in the elafibranor group, compared to a change from 99.26%, 97.55%, and 95.49% at baseline to 99.2%, 97.35%, and 95.12% in the placebo group.

For the GLOBE score at Week 52, the median (IQR) change from baseline was -0.40 (-0.63; -0.08) for elafibranor and 0.09 (-0.17; 0.28) for placebo. Based on the GLOBE score, the median estimated transplant-free survival rates at 5, 10, and 15 years increased from 96.63%, 91.19%, and 84.77% at baseline to 97.78%, 94.12%, and 89.71% at 52 weeks in the elafibranor group, compared to a change from 97.03%, 92.21%, and 86.47% at baseline to 97.19%, 92.62%, and 87.15% at Week 52 in the placebo group.

Considering the additional analysis related to pruritis (Worst Itch NRS score, sustained improvement, worsening of pruritus and 5-D Itch Score) some results did indicate a worsening of pruritis under elafibranor treatment.

Fatigue and QoL questionnaires did either not indicate a clinically relevant difference or the clinical relevance of the observed changes was not self-evident.

Histological information (biopsies) was available in a limited number of patients 57/161 (35.4%). Changes in fibrosis score (Nakanuma) did not identify relevant differences between treatment groups after 52 weeks of treatment.

Biomarker related to inflammation (haptoglobulin and fibrinogen) or immune response (IgM and IgG) did not show clinical relevant changes. Also, for the non-invasive biomarkers of hepatic fibrosis (by ELF test (which combines measurements of HA, type 3 procollagen peptide [PIIINP], and TIMP-1), PAI-1, TGF-β, CK-18 (M65 and M30), and Pro-C3) did not show notable differences. Additional analysis of lipid related parameters (TC, LDL-C, calculated VLDL-C, TG and HDL-C) and bile acid related parameters did not show any clinically relevant effect although the effect on the C4 and GF-19 (bile acid related parameters) showed some trend to improvement.

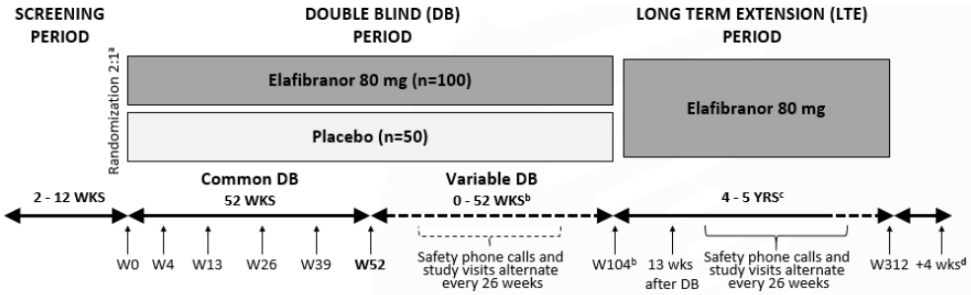
- **Ancillary analyses**

No ancillary analysis for efficacy were performed

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16: Summary of efficacy for trial GFT505B-319-1

<table>
<tr><td colspan="3"><u>Title:</u> A double-blind, randomised, placebo-controlled study and open label long term extension to evaluate the efficacy and safety of elafibranor 80 mg in patients with primary biliary cholangitis with inadequate response or intolerance to ursodeoxycholic acid</td></tr>
<tr><td>Study identifier</td><td colspan="2">GFT505B-319-1
European Clinical Trials Database (EudraCT) Number:</td></tr>
<tr><td>Design</td><td colspan="2">Phase III, randomised, double-blind, placebo-controlled, parallel-group study followed by an open-label long-term extension (LTE) evaluating the efficacy and safety of elafibranor in participants with PBC and inadequate response or intolerance to UDCA.
Participants were randomised in a 2:1 ratio to receive elafibranor 80 mg or placebo, once daily, during the common DB period (the first 52 weeks of treatment period) and up to a maximum of 104 weeks (the overall DB period). At the time of data cut-off for the Study 319-1 CSR (01 June 2023), the last participant had completed their Week 52 visit. The LTE period remains ongoing. When applicable, participants continued their pre-study dose of UDCA throughout the study participation.
 
</td></tr>
<tr><td></td><td>Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>52 weeks
not applicable
4 to 5 years</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority; the lower limit of the two-sided 95% CI for the risk difference in responders is above 0%</td></tr>
</table>

Title: A double-blind, randomised, placebo-controlled study and open label long term extension to evaluate the efficacy and safety of elafibranor 80 mg in patients with primary biliary cholangitis with inadequate response or intolerance to ursodeoxycholic acid			
Study identifier	*GFT505B-319-1* European Clinical Trials Database (EudraCT) Number:		
Treatments groups	Elafibranor group		Elafibranor 80 mg daily for 52 weeks DB with a variable DB phase of 0 to 52 week and a OLE of 4 to 5 years, N=108
	Placebo		placebo for 52 weeks DB with a variable DB phase of 0 to 52 week, N= 53
Endpoints and definitions	Primary endpoint	Risk difference in cholestasis composite response at week 52	Cholestatis composite response at Week 52 is defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15% with patients who discontinued treatment are considered as non-responder. Difference in percentage of cholestatis composite response at week 52 after treatment with Elafibranor compared to after treatment with placebo.
	First key secondary endpoint	Risk difference in ALP normalisation composite response at week 52	ALP normalisation composite response at week 52 is defined as ALP<ULN. with patients who discontinued treatment are considered as non-responder. Difference in percentage of ALP normalisation response at week 52 after treatment with Elafibranor compared to after treatment with placebo
	Second key secondary endpoint	Difference in Pruritis change from baseline to week 52	Difference in pruritus change from baseline through Week 52 between the elafibranor arm and the placebo arm, based on PBC Worst Itch NRS in participants with baseline PBC Worst Itch NRS score ≥4
Database lock	16 June 2023		
Results and Analysis			
Analysis description	**Primary Analysis:** The primary efficacy analysis is based on the exact Cochran-Mantel-Haensel (CMH) test stratified by the randomization factors, where the estimated risk difference is a stratum-adjusted risk difference with CMH weights and using the Newcombe method for the calculation of the 95% CI. For consistency, the 95% CIs for the single proportions are based on the Wilson score method.		
Analysis population and time point description	Intent to treat: all randomised patients Pruritus ITT Analysis Set: All patients from the ITT analysis set with baseline PBC Worst Itch NRS score ≥4. Analysis time point is at 52 weeks		
Descriptive statistics and estimate variability	Treatment group	elafibranor	placebo
	Number of subjects biomarkers	108	53
	Cholestasis composite response, n (%)) 95% CI (%)	55 (50.9) (41.6, 60.2)	2 (3.8) (1.0, 12.8)
	ALP normalisation composite response, n (%)	16 (14.8)	0 (0.0)
	Number of subjects Pruritis	44	22

Title: A double-blind, randomised, placebo-controlled study and open label long term extension to evaluate the efficacy and safety of elafibranor 80 mg in patients with primary biliary cholangitis with inadequate response or intolerance to ursodeoxycholic acid			
Study identifier	*GFT505B-319-1* European Clinical Trials Database (EudraCT) Number:		
	Mean pruritis at baseline (SD)	6.19 (1.50)	6.25 (1.15)
	Least square mean pruritis change from baseline in week 52 (95% CI)	-1.93 (-2.60; -1.26)	-1.15 (-2.14; -0.15)
Effect estimate per comparison	Primary endpoint	Comparison groups	Elafibranor and Placebo group
		Risk difference (%)	47.2
		95% Confidence interval (%)	(32.0, 56.9)
		P-value (stratified CMH test	< 0.0001
	First Key Secondary endpoint	Comparison groups	Elafibranor and Placebo group.
		Risk difference	14.8
		95% confidence interval (%)	(6.1, 22.7)
		P-value (CMH test)	< 0.0019
	Second Key Secondary endpoint	Comparison groups	Elafibranor and Placebo group.
		LS Mean difference	-0.78
		95% Confidence interval	(-1.99, 0.42)
		P-value (MMRM analysis)	0.19
Notes	A composite strategy was chosen for the primary and first key secondary endpoint: Patients who discontinued treatment are considered as non-responder. Missing values at week 52 without an intercurrent event are replaced by the closest non-missing assessment. The fixed-sequence testing approach was used to control the overall type I error. The testing stopped after testing the second key secondary endpoint.		

2.6.5.3. Clinical studies in special populations

For pivotal Study 319-1, subgroup analyses of the primary endpoint and first key secondary endpoint were performed based on age, sex, race, UDCA treatment at baseline, prior OCA treatment, ALP level at baseline >3 x ULN, TB at baseline >ULN, TB at baseline >ULN or ALB at baseline <LLN, TB at baseline >0.6 x ULN, geographic region, ALP >3 x ULN or TB >ULN at baseline, PBC Worst Itch NRS score ≥4 at baseline, cirrhosis, and advanced disease stage. Subgroup analyses demonstrated a consistent cholestatic treatment effect in favour of elafibranor across the subgroups including participants with ALP >3 x ULN, TB >0.6 x ULN, advanced fibrosis, and by age (<65 years, ≥65 years) and geographic region.

Subgroup analyses of the primary efficacy endpoint performed on the ITT. Both treatment (elafibranor 80 mg and placebo) groups were well balanced with respect to the distribution of participants within the subgroups. Overall, the majority of the participants were females (95.7%), White (91.3%), aged <65 years (78.3%), received concurrent UDCA treatment (95.0%), without prior OCA treatment

(91.9%), and were from sites in Europe (34.8%) and North America (42.9%). At baseline, a total of 39.1% of participants had ALP >3 x ULN, 24.8% had TB >0.6 x ULN, 3.7% had TB >ULN at baseline and none (0%) had ALB <LLN.

Subgroup analyses demonstrated a consistent cholestasis treatment effect in favour of elafibranor 80 mg among various participant subsets, including participants with ALP >3 x ULN, TB >0.6 x ULN, advanced fibrosis, without prior OCA treatment, on current UDCA treatment, PBC Worst Itch NRS score ≥4 or by age and geographical region.

Subgroup analyses of the first key secondary efficacy endpoint performed on the ITT Analysis Set. Subgroup analyses of the first key secondary endpoint demonstrated a consistent treatment effect in favour of elafibranor 80 mg among various participant subgroups that were generally consistent with subgroup analyses performed on the primary endpoint.

A higher treatment response on ALP normalisation was observed in participants on elafibranor 80 mg aged ≥65 years (24.0%; none with placebo) compared to those aged <65 years (12.0%; none with placebo), while a lower treatment response was observed in participants with baseline ALP >3 x ULN (4.7%; none with placebo) compared to those with ALP ≤3 x ULN (21.5%; none with placebo); a similar trend was noted for participants with baseline ALP >3 x ULN or TB >ULN compared to those with ALP ≤3 TB >ULN compared to those with ALP ≤3 x ULN TB <ULN.

A lower treatment response was observed in participants with baseline LSM >10 kPa and/or bridging fibrosis or cirrhosis on histology consistent with advanced disease (8.6%, none with placebo) compared to the overall ITT population (14.6%; none with placebo).

Among the 6 participants with moderately advanced disease according to Rotterdam criteria (TB >ULN or ALB <LLN) (4 and 2 on elafibranor 80 mg and placebo, respectively), or the 16 cirrhotic participants based on LSM ≥16.9 kPa and/ or cirrhosis on liver histology (9 and 7, respectively), or the 8 participants not on UDCA at baseline and therefore receiving elafibranor 80 mg or placebo monotherapy (6 and 2, respectively), none achieved ALP normalisation either in the elafibranor 80 mg or placebo groups.

2.6.5.4. Supportive study(ies)

This application is based on one pivotal trial. Supportive evidence derived from the dose fining phase 2 study 216-1 as described further above.

2.6.5.5. Patient engagement

Based on information provided by the Dutch collective of liver patients (Nederlandse Leverpatiënten Vereniging (NLV)) on their website the most cumbersome signs or symptoms are pruritis, fatigue and "brain fog". In patients with some further developed disease icterus, xanthomata, increased cholesterol and fatty diarrhoea. Additionally, a considerable portion of the patients suffers from other autoimmune diseases such a Sjogren syndrome, rheumatic arthritis or psoriasis.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical programme consists of one pivotal study (study 319-1) and one phase 2b dose-finding study (study 216-1) both studies together included 206 patients. This is a very limited number of patients. However, given the rarity of the disease this is considered acceptable.

The patients were diagnosed according to the latest diagnostic guidelines and represent a reasonable sample of the population intended to be treated.

The Phase 2, double-blind, randomised, parallel group, placebo-controlled, clinical study (216-1) was primarily conducted in order to evaluate the efficacy of elafibranor 80 mg and 120 mg in subjects with PBC as measured by relative change from baseline in serum ALP levels. This study also evaluated several secondary efficacy objectives including changes from baseline in GGT, 5'nucleotidase, total and conjugated BIL, ALB, ALT, AST, lipid parameters, bile acids, inflammatory and liver fibrosis markers, pruritus VAS, and responses on the PBC-40 QoL questionnaire; the proportion of responders based upon reduction in ALP; response to treatment based on normalisation of ALP, BIL, ALB, and composite endpoints (evaluating changes in both ALP and total BIL). In addition, several safety objectives were evaluated, and an exploratory PK analysis was performed.

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 consists of a 2- to 12-week screening period, a 52- to 104-week DB period, followed by a 4- to 5-year LTE period, and a 4-week safety follow-up period after the last dose of study treatment. When applicable, participants continued their pre-study dose of UDCA throughout the study participation. The study design included a 52-week DB period (referred to as the common DB period) that was completed by all participants, followed by a variable DB period where participants continued to receive elafibranor or placebo until the last participant completed their Week 52 visit or the participant received 104 weeks of treatment, whichever came first.

Since no treatment alternative for PBC second line treatment was available at the start of the study, a placebo comparison is considered acceptable. The endpoints defined in the study protocol of study 319-1 are in line with both the latest guidance and the scientific advice, and as such acceptable.

The duration of the study (1 year) is in line with the regulatory EMA guidance at the time of the start of the study (319-1) (Draft reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases, PBC, PSC, NASH; EMA/CHMP/299976/2018) and as such acceptable. However, in the latest guidance (Reflection paper on regulatory requirements for the development of medicinal products for primary biliary cholangitis, PBC, and primary sclerosing cholangitis, PSC; EMA/CHMP/299976/2018) a study duration of two years is advised.

Efficacy data and additional analyses

Dose-finding study

In total, 45 adult subjects with PBC met the in- and exclusion criteria in **study 216-1** and were randomised to the study treatments on a 1:1:1 basis (elafibranor 80 mg, elafibranor 120 mg, or placebo). The 3 treatment groups had similar demographic and baseline characteristics, which were representative of the clinical PBC population. On the basis of the Rotterdam criteria (based BIL and ALB values within ULN), all subjects randomised in this study can be considered to be within the early stages PBC.

On the anticholestatic activity, both elafibranor doses produced statistically significant reductions in ALP compared with the subject's receiving placebo. There was no apparent difference in the magnitude of improvement between the 2 elafibranor doses suggesting a plateau of the dose-exposure-response. The effect was observed from the first visit following baseline (Visit 2) and was maintained up to the end of the active treatment period.

The response rate to treatment on the composite endpoint "ALP < 1.67 × ULN, total BIL within normal limits, and > 15% ALP reduction" from baseline to 12 weeks was higher in both elafibranor treatment groups (66.7% and 78.6%, respectively) compared to placebo (6.7%). These positive results were confirmed by other secondary endpoints such as ALP normalisation from baseline to endpoint and the proportion of subjects with at least a 10%, 20%, or 40% decrease in ALP from baseline to endpoint. The reductions in γGT and 5'nucleotidase levels from baseline to end of study (in either mean relative change or mean absolute change) were also higher for the elafibranor vs placebo comparisons (exception: not for 5'nucleotidase for the 120 mg dose level; however, the treatment effects were similar to the 80 mg dose level) and confirmed that the ALP effect was of hepatic origin. The effect on γGT and 5'nucleotidase levels was observed from the first visit following baseline (Visit 2) and was maintained and reinforced up to the end of the active treatment period. However, when the effect on ALP is defined as normalisation or as the composite endpoint used in the phase 3 trial (ALP <1.67 x ULN, TB ≤ULN and ≥15% ALP reduction) this was more pronounced in the arm with the 120 mg dose as compared to the 80 mg.

In addition, the elafibranor anti-inflammatory treatment effect was observed by the measurable reduction in IgM, CRP, haptoglobin, and fibrinogen levels from baseline to 52 weeks in both elafibranor treatment groups compared to placebo. A reduction in levels of C4, an intermediate in bile acid synthesis, from baseline to endpoint was observed with both elafibranor doses, indicating an inhibition of bile acid synthesis; C4 levels increased from baseline to endpoint in the placebo group.

The beneficial effect of elafibranor on metabolic parameters indicated a reduction of total cholesterol, LDL-C, and triglyceride levels while HDL-C levels remained unchanged.

Plasma concentrations and PK parameters measured for GFT505 and GFT1007 in subjects with PBC were similar with that measured in healthy volunteers in previous studies with comparable dose regimen. The results obtained in the phase II study 216-1 suggests that the PK of GFT505 and its active metabolite (GFT1007) are not modified in subjects with PBC. In addition, with the PopPK analysis no clinically relevant effect of population on the PK of elafibranor or GFT1007 could be seen suggesting that no dose adjustment between healthy participants and PBC participants would be required.

There was no worsening of pruritus with elafibranor. There were 3 TEAEs of pruritus reported within each of the 3 treatment groups. On the contrary, a higher relative reduction from baseline to endpoint in the pruritus VAS scoring values was demonstrated for both elafibranor 80 mg and 120 mg treatment groups compared to the placebo treatment group. Further, an improvement in terms of QoL as measured by the median relative change from baseline to endpoint in the pruritus domain of PBC 40-QoL questionnaire is reported.

In conclusion, there was no apparent difference in the magnitude of improvement between the 2 elafibranor doses suggesting a plateau of the dose-exposure-response.

Pivotal study

The pivotal **Study 319-1** was a multicentre, multinational, randomised (2:1), double-blind (DB), placebo-controlled, parallel-group phase III study followed by an open-label LTE evaluating the efficacy and safety of elafibranor 80 mg *die* in participants with PBC with inadequate response or intolerance to UDCA. The study design is considered adequate for the objectives and in line with the relevant EMA GL (EMA/CHMP/299976/2018).

The in- and exclusion criteria are overall acceptable, but some restrictions, such as those on health conditions and concomitant medicines, might diminish the generalisability of the results.

Overall, 108 participants were included in the elafibranor ITT Analysis Set, and 53 participants were included in the placebo ITT Analysis Set.

Subjects had a mean time since PBC diagnosis of 8.0 years with no unexpected or evident imbalances in baseline characteristics between the study arms, except a trend toward higher biochemical liver markers (ALP, ALT and GGT) median baseline values in elafibranor arm (ALP: 296.5 U/L vs 254.0 U/L). Almost all subjects (96.3%) had a baseline ALP >1.67 x ULN (therefore, results of the composite primary endpoint were driven by this component), and 39.1% had a baseline ALP >3 x ULN. The majority of participants (96.3%) had a baseline TB level ≤ULN. Therefore, results of the composite primary endpoint are not influenced by this component. In addition, a subset of patients had advanced disease as per LSM >10 kPa (assessed by fibroscan) and/or bridging fibrosis or cirrhosis on histology (35, 33.7% and 19, 38.0% of participants, respectively, on elafibranor 80 mg and on placebo.

At baseline, 41.0% of subjects had a PBC Worst Itch NRS score of ≥4 with no differences between the treatment groups.

Overall, the included population reflects the typical early PBC population with a subgroup representative of more advanced disease.

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%, that, although not validated, is an intermediate measure of effect used in PBC setting and reported in current EMA GL. The actual clinical relevance of such endpoint and the predictive value on clinical benefit remains to be demonstrated for elafibranor.

The Key secondary endpoint was ALP normalisation which is also recommended by EMA GL as a more stringent endpoint; among other stricter endpoints there are: ALP <1.5 x ULN, ALP decrease ≥40% and TB≤ULN, all evaluated as secondary endpoints.

The second and third key secondary endpoints were aimed at evaluating elafibranor effect on pruritus, commonly reported in PBC patients due to cholestasis. The type-1 error control and the fixed-sequence testing procedure was applied for the primary and key secondary endpoints; for the other secondary endpoints statistical testing was exploratory in nature.

Other relevant secondary and exploratory endpoints were overall acceptable. Clinical events were also recorded, as well as histological evaluation when available.

Overall, the statistical analysis is acceptable, and several sensitivity analyses were performed to evaluate the robustness of the results. For the primary estimand and the first key secondary estimand a composite strategy was used to handle the intercurrent events (ICEs); therefore, subjects who discontinued treatment or used rescue therapy were considered treatment failure (i.e. non-responders). When including the additional ICEs, the results were similar to the original submitted analyses for the primary endpoint of cholestasis response and the secondary endpoint of ALP normalization.

Results

Regarding the **primary endpoint** (composite biochemical endpoint i.e. ALP <1.67 x ULN and TB ≤ULN and ALP decrease ≥15%) at Week 52, the proportion of responders was 55/108 (50.9%) participants in the elafibranor group compared with 2/53 (3.8%) participants 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 were similar using the PP Analysis Set. The results are robust as demonstrated by various sensitivity and supplemental analyses.

The first key **secondary endpoint,** ALP normalisation at week 52, showed that the responders were more in elafibranor group (14.8%) than placebo (0.0%, [exact CI: 5.5; 23.0] p=0.0019) thus reaching the statistical significance; however, normalisation of ALP, which would be the optimal goal to achieve (although a clear predictive value on long term outcome is not established), is seen only in a limited subset of patients (roughly 15%).

The **second and third key secondary endpoints** were aimed at evaluating improvement of pruritus, a common symptom in PBC, measured as a change from baseline in pruritus through Week 52 and Week 24. The analysis was conducted in the Pruritus ITT Analysis Set (n=44 elafibranor vs 22 placebo) who had moderate to severe pruritus with a baseline PBC Worst Itch NRS score ≥4 (mean±SD baseline score of 6.2±1.50 and 6.3±1.15). Results did not reach the statistical significance, although a trend in decrease from baseline in the PBC Worst Itch NRS score was observed in the elafibranor group (-1.9; 95%CI -2.6, -1.3) compared with placebo (-1.1; 95%CI -2.1, -0.2). Similar results were observed at Week 24 and also in the ITT analysis set.

Supplementary analyses evaluating the proportion of participants achieving at least 1-point, 2-points, or 3-points decrease in PBC Worst Itch NRS score from baseline at weeks 24 and 52 were consistent with this trend. Results from analysis of the 5D Itch Total score were similar.

Thus, in summary, there seems to be a trend towards pruritus improvement, but of modest entity at best. Provided efficacy data on pruritus are neither considered statistically significant nor clinically relevant.

Other secondary endpoints descriptively evaluating the biochemical response in elafibranor treated patients as compared to PLB according to different definitions have been performed.

Results favouring elafibranor versus PLB were also seen using different percentage cut-offs of ALP (alone) reduction at week 52: ALP reduction ≥10% (75.5% vs 22.6%), ≥20% (69.8% vs 5.7%), and ≥40% (54.7% vs 0%). Using a more stringent response than the primary endpoint (composite: ALP <1.5xULN, ALP decrease from baseline ≥40% and TB ≤ULN) this was achieved in 38% of participant receiving elafibranor and 0% in placebo.

Concerning hepatic biochemical measures of response including total bilirubin (TB), the other component of the primary composite endpoint, measured according to different definitions (TB ≤ULN and/or ALB ≥LLN, a 15% decrease in TB from baseline, TB ≤0.6 ULN, TB ≤ULN or no increase from baseline >0.1xULN), comparable results were observed in the treatment and placebo groups. Thus, TB was mainly unaffected by elafibranor treatment (change from baseline: -0.12 umol/L vs 1.14 in placebo): this is expected since almost all patients had normal baseline TB levels. The limited effect on TB (being this a predictor of PBC progression) casts some doubts on the clinical efficacy of elafibranor, especially in advanced/at risk patients.

Several composite endpoints including ALP and TB have been evaluated, with different cut-offs with respect to the primary endpoint; overall, the trend was in favour of elafibranor versus placebo. However, results are mainly driven by the effect on ALP since bilirubin levels were within normal ranges in the majority of patients, and only a subgroup was representative of moderately advanced PBC or at risk of progression.

Analysis based on the PBC Risk Scores and median **estimated** transplant-free survival rates: at Week 52, the median (IQR) change from baseline in the UK-PBC score was -0.29 (-0.60; 0.06) for participants on elafibranor and 0.09 (-0.32; 0.42) for placebo. At Week 52, the 5-, 10-, and 15-year survival rates increased from 99.19%, 97.32%, and 95.07% at baseline to 99.46%, 98.19%, and 96.65% in the elafibranor group, compared to a change from 99.26%, 97.55%, and 95.49% at baseline to 99.2%, 97.35%, and 95.12% in the placebo group. For the GLOBE score at Week 52, the median (IQR) change from baseline was -0.40 (-0.63; -0.08) for elafibranor and 0.09 (-0.17; 0.28) for

placebo. Based on the GLOBE score, the median estimated transplant-free survival rates at 5, 10, and 15 years increased from 96.63%, 91.19%, and 84.77% at baseline to 97.78%, 94.12%, and 89.71% at 52 weeks in the elafibranor group, compared to a change from 97.03%, 92.21%, and 86.47% at baseline to 97.19%, 92.62%, and 87.15% at Week 52 in the placebo group. These initial results are not mature enough to make firm conclusions thus, the clinical relevance remains to be established. As this application is for a CMA, the post authorisation follow-up as laid down in the SOB will provide further data to evaluate the clinical relevance of the observed effects. In addition to the confirmatory evidence to be provided in the SOB (see below) the pivotal **study 319**-1 entails an LTE open label period (4-5 years), during which the patients from the DB period will receive elafibranor; clinical outcomes will be collected (even if with no placebo control arm); this LT extension is supported and data will on this category 3 study be provided as described in the risk management plan post-authorisation.

At Week 52, participants treated with elafibranor had reductions in haptoglobin compared to participants who received placebo (ITT Analysis Set), with an estimated LS mean change from baseline of -0.166 g/L in the elafibranor group and -0.001 in the placebo group (estimated LS means difference between groups: -0.165 (95% CI: -0.285; -0.044). The estimated LS means change from baseline in hsCRP at Week 52 was 0.81 mg/L in the elafibranor group and 1.02 (mg/L) in the placebo group, with an estimated LS means ratio of 0.79 (95% CI: 0.63; 1.00). For fibrinogen, the estimated LS means change from baseline at Week 52 was -1.007 g/L in the elafibranor group and -0.769 g/L in the placebo group (LS means difference between groups: -0.238 (95% CI: -0.642; 0.166). The estimated LS means change from baseline at Week 52 for TNF-α was -2.031 pg/mL in the elafibranor group and -2.137 pg/mL in the placebo group (estimated LS means difference between groups: 0.105 (95% CI: -0.510; 0.721).

An exploratory analysis was conducted to evaluate changes in fibrosis (nakanuma score) in patients with available liver biopsy. A total of 57/161 (35.4%) participants consented to have an optional liver biopsy, of which 47 participants underwent a baseline biopsy (31 participants on elafibranor and 16 participants on placebo) and 40 had a Week 52 biopsy (30 participants on elafibranor and 10 participants on placebo). Overall, 35 participants had a paired baseline and Week 52 biopsy (25 participants on elafibranor, 10 participants on placebo). An improvement in fibrosis score (nakanuma) was seen in 7/25 (28.0%) participants in the elafibranor group compared to 1/10 (10%) in the placebo group. There was no change in fibrosis score in 11/25 (44.0%) participants in the elafibranor group and 9/10 (90.0%) participants in the placebo group. Overall, interpretation of score shifts is hampered by the very limited number of patients tested and thus no effect on fibrosis could be inferred at this point. Moreover, a non-invasive measurement of liver fibrosis by ELF (panel of 3 serum biomarkers giving a score reflecting severity of liver fibrosis) was not significantly different between the two arms. Due to the slow progression of PBC, longer exposure to the drug and more patients undergoing to fibrosis assessment are deemed necessary, this will be followed-up post authorisation in the study made SOB to this conditional marketing authorisation.

Only few data on relevant clinical outcomes are submitted within the present MAA; a total of 3 clinical events in 2 elafibranor participants occurred within 52 weeks of treatment (MELD Na >14, Uncontrolled ascites requiring treatment, Death). Other four participants had events (1 in the elafibranor and 3 in the placebo group), between Week 52 and up to Week 104. The numbers are very few to draw any conclusions, and the results on the long-term clinical outcomes defining the real benefit of a drug used in PBC treatment are still necessary to confirm elafibranor efficacy.

A variety of PRO measures were evaluated: except for a measure of fatigue (PROMIS Fatigue SF 7a questionnaire) showing a slight improvement in elafibranor treated patients with clinical relevance to be established, all the other outcomes did not show meaningful differences.

Subgroup analyses

There appears to be a limited cholestatic/biochemical response at week 52 for the subjects with more advanced PBC. Further analyses have been performed to analyse the primary endpoint and key secondary endpoints according to stratification by pruritus and ALP or total bilirubin (TB) levels at baseline. From the analyses it seems that pruritus at baseline (according to PBC Worst Itch NRS score ≥ 4) has small or no impact on the efficacy, whereas the strongest determinant of response to elafibranor was represented by the other stratification variables: ALP > 3x ULN or TB > ULN. Further information would be collected with the long term ELFIDENCE study.

Subgroup analyses were performed for primary and key secondary endpoints, including ALP/TB levels at baseline. Patients with ALP >3xULN at baseline had a markedly lower probability of response to elafibranor compared to patients <3xULN (20.9 vs 70.8%) but higher than the respective placebo subgroups (0 vs 6.1%). Similar data are observed when considering subjects with moderately advanced PBC (i.e. baseline TB >ULN or ALB <LLN as per Rotterdam Criteria): in this subgroup no patients responded, but the number of subjects meeting this criterion in the elafibranor arm was only 2; patients without Rotterdam Criteria had a probability of responding of 52.9% (versus 3.9% in placebo). When considering PBC patients at risk of progression (i.e. TB >0.6 x ULN), responders were again less in the high-risk group compared to the lower one (29.6 vs 58.0%). Cirrhotic patients were few, but it seems evident that responders were less in the group with this complication (n/N: 1/9) compared to subject without (n/N, %: 54/99, 54.5%); for comparison, the non-cirrhotic responder in placebo were 4.3%. Advanced disease stage patients (defined as having at baseline LSM >10 kPa on Fibroscan exam and/or bridging fibrosis or cirrhosis on histology) showed a slightly lower response rate compared to patients without this criterion (45.7 vs 53.4%).

Monotherapy: The applicant is claiming elafibranor indication also as monotherapy in PBC patients unable to tolerate UCDA based on data coming from only 8 patients (6 received elafibranor and 2 placebo) enrolled in study 319-1. For only 4 out of 6 patients are data availible at the end of the study: in three of these, an ALP reduction was observed (ranging from –90 to –182 U/L) but only one was considered responder based on the endpoint definition; in the remainingpatient an increase of 215 U/L was seen. No additional data or studies using elafibranor in monotherapy have been submitted. Given the rarity of the disorder and the even greater rarity of UDCA intolerance (estimated 3-5% of patients) is acknowledged that providing fully comprehensive evidence pre-authorisation may not be feasible. Importantly, in PBC patients not tolerating UDCA a high unmet need is recognised. Therefore, it is agreed that elafibranor can be used as monotherapy in patients unable to tolerate UDCA. Further data on the monotherapy setting will also become available with the results of the non-interventional study (CLIN-60190-461 (ELFINITY) which is a category 3 study in the RMP.

Additional efficacy data needed in the context of a conditional MA

The provided efficacy data are mainly based on results of the primary endpoint that 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%, that, although not validated, is an intermediate measure of effect used in PBC setting and reported in the current EMA reflection paper on PBC. The actual clinical relevance of such endpoint and the predictive value on clinical benefit for elafibranor remains however to be demonstrated. The data provided on biochemical response in the monotherapy setting is considered particularly sparse but acceptable given the rarity of the disorder and the even greater rarity of UDCA intolerance (estimated 3-5% of patients).

Only few data on relevant clinical outcomes are submitted within the present MAA; a total of 3 clinical events in 2 elafibranor participants occurred within 52 weeks of treatment (MELD Na >14, Uncontrolled ascites requiring treatment, Death). Other four participants had events (1 in the elafibranor and 3 in the placebo group), between Week 52 and up to Week 104. The numbers are very few to draw

conclusions, and the results on the long-term clinical outcomes defining the real benefit of a drug used in PBC treatment are still necessary to confirm elafibranor efficacy post authorisation.

As comprehensive data on clinically relevant endpoints are considered to be needed for a full approval the applicant requested a conditional approval. Therefore, the applicant proposes to submit information on clinically relevant endpoints (metabolic decompensation, liver transplantation or death, etc.) as condition for the marketing authorisation.

The applicant proposes an ongoing phase III, randomised, parallel-group, double-blind, placebo-controlled, multicentre, event-driven study to evaluate the efficacy of elafibranor 80 mg/day in adult with PBC, up to 84 months (**study 454**; EU CT: 2023-505251-43-00) including PBC patients with more advanced disease. Approximately 450 eligible participants are proposed to be randomised 2:1 to elafibranor or placebo (stratified based on cirrhosis status at baseline: no cirrhosis, cirrhosis not Child Pugh B, and cirrhosis Child Pugh B). The primary endpoint is event-free survival, as time to the first occurrence of any of the following: all-cause mortality, liver transplant, liver decompensation, change in MELD-Na score to ≥15, development of hepatocellular carcinoma; the primary endpoint and the clinical events chosen are deemed appropriate to gather significant clinical information on the efficacy of elafibranor. Other endpoints will evaluate progression to cirrhosis, changes in biochemical markers, including the surrogate endpoints used in the data already provided. The study is in its initial stages and no results have been provided during the current procedure and will also provide further data in the monotherapy setting.

2.6.7. Conclusions on the clinical efficacy

The results reported for elafibranor show response on the most relevant biomarkers predictive for clinical efficacy in PBC and the combinations thereof. However, the effect is mainly exerted on ALP leading to normalisation of this biomarker only in a subgroup of PBC patients; the effect shown on the bilirubin component is minimal. The clinical relevance of the observed biochemical changes, as well as their validity as surrogate markers, remains to be demonstrated.

For the predictive models (UK-PBC and Global-PBC), indicators for inflammation, indicators of fibrosis and histology measurement results were reported indicative of efficacy in the claimed indication. Given the short time of the treatment (52 weeks) during the pivotal study it is however not to be expected that any of these parameters show a clear clinically relevant effect. No consistent clinical effect was observed for the symptomatic treatment (pruritus, fatigue and QoL).

Provided results including clinical data and relevant biomarker changes indicate that treatment with elafibranor may translate into a clinically relevant benefit in the claimed indication. This is requested to be confirmed by means of a clinical study within the scope of this conditional marketing authorisation. The condition is intended to provide long-term clinical outcome data including data in the more advanced liver disease population.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

Description	**Due date**
In order to confirm the efficacy and safety of elafibranor in 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, the MAH shall conduct and submit the final results of the phase III randomised, parallel-group, double-blind, placebo-controlled, two-arm study (ELFIDENCE) to evaluate the efficacy and safety of elafibranor on long-term	May 2030

Description	Due date
clinical outcomes in adults with Primary Biliary Cholangitis (PBC).	

2.6.8. Clinical safety

Overview of clinical safety data on elafibranor

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.

Data from studies in the PBC indication are supplemented with safety data from studies in other indications (hepatic and non-hepatic). The hepatic indications include studies in participants with non-alcoholic steatohepatitis (NASH)(Phase 3 study GFT505-315-1, Phase 2 study GFT505-212-7, and Phase 2 study GFT505e-218-1) and non-alcoholic fatty liver disease (NAFLD)(Phase 2 study GFT505-219-8). The non-hepatic indications include obesity and/or abnormal glucose tolerance, diabetes mellitus, and dyslipidaemia/hyperlipidaemia.

All studies on elafibranor were conducted under Good Clinical Practice (GCP) guidelines.

The safety parameters evaluated in the elafibranor clinical studies included the following:

- adverse events
- treatment-emergent adverse events including fatal events, serious treatment-emergent adverse events, treatment-emergent adverse events leading to withdrawal, treatment-emergent adverse events relating to pregnancy
- clinical laboratory tests (haematology, clinical chemistry, urinalysis)
- vital signs (e.g. blood pressure, heart rate, respiratory rate, body temperature)
- body weight and body mass index (BMI)
- 12-lead electrocardiograms (ECGs)
- physical examinations (note: postbaseline abnormalities in physical examination findings were generally recorded as adverse events)

Additional safety assessments were performed in selected studies (e.g. studies in participants with obesity/abnormal glucose intolerance, type 2 diabetes, dyslipidaemia/hyperlipidaemia).

Safety data of separate studies were not pooled.

2.6.8.1. Patient exposure

The elafibranor clinical development program currently comprises a total of 31 clinical studies.

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.

In the double-blind treatment period of study 319-1, the clinical effects of once daily administration of elafibranor 80 mg compared with placebo (randomisation ratio 2:1) in 161 participants with PBC with inadequate response or intolerance to ursodeoxycholic acid (UDCA) with a maximum treatment duration of 104 weeks. The open label long-term extension period of this study is ongoing and is expected to last for a maximum of 5 years. The 12-week Phase II study 216-1 evaluated 2 doses of

elafibranor compared with placebo in 45 participants with PBC with an inadequate response to UDCA (randomised 1:1:1 to placebo, elafibranor 80 mg, or elafibranor 120 mg).

Safety data from studies in the PBC indication are supplemented with safety data from participants in other indications who received elafibranor, including hepatic and non-hepatic indications. The hepatic indications include studies in participants with non-alcoholic steatohepatitis (NASH) (Phase 3 study GFT505-315-1, Phase 2 study GFT505-212-7, and Phase 2 study GFT505e-218-1) and non-alcoholic fatty liver disease (NAFLD) (Phase 2 study GFT505-219-8). The non-hepatic indications include obesity, diabetes mellitus, and dyslipidaemia.

Several studies were conducted in special populations: one study in participants with renal impairment, one study in participants with hepatic impairment, one study in elderly participants (≥75 years), and one thorough QT study.

Overall exposure

Participant exposure from all studies completed with elafibranor across all indications is presented in **Table 17**.

Cumulative participant exposure to elafibranor, regardless of the indication, is presented in **Table 18** by age and sex, in **Table 18** by elafibranor dose received, and in **Table 19** by duration of exposure. Participant exposure specifically from the studies with elafibranor in adults conducted in PBC indication is presented in **Table 23.**

Overall, a total of 3,745 participants have been enrolled in the elafibranor clinical programme since the Development International Birth Date (DIBD, 01 August 2006) until the data cut-off (01 June 2023) of whom 2,588 have been exposed to elafibranor until the current data cut-off (01 June 2023), based on actual exposure data from completed clinical trials (excludes data from the currently ongoing studies CLIN 60190 450, CLIN-60190-453, and CLIN-60190-454). 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.

Table 17: Overall exposure in studies completed with elafibranor across all indications

Study details				**Number of participants Treated**		
Study indication		**Study ID**	**Phase**	**Elafibranor**	**Placebo**	**Total**
Primary indication	**PBC**	**Total**		**138**	**68**	**206**
		GFT505B319-1 [a]	3	108 [f]	53 [f]	161
		GFT505b 216-1	2	30	15	45
Other indications	**Hepatic indications**					
	NASH	**Total**		**1,625**	**809**	**2,434**
		GFT505-315-1 [b]	3	1,433 [f]	717	2,150
		GFT505-212-7	2b	182	92	274

Study details				Number of participants Treated		
Study indication		**Study ID**	**Phase**	**Elafibranor**	**Placebo**	**Total**
		GFT505e-218-1 [c]	2a	10	-	10
	NAFLD	GFT505-219-8	2	**13**	**13**	**17 [d]**
	Non-hepatic indications					
	Diabetes mellitus	**Total**		**59**	**50**	**109**
		GFT505-210-5	2a	50	47	97
		GFT505-111-7 (Part 4)	1	9	3	12
	Obesity/overweight and/or abnormal glucose tolerance	**Total**		**90**	**61**	**129**
		GFT505-209-4	2a	23	24	47
		GFT505-210-6	2a	22	22	22 [e]
		GFT505-111-7 (Part 2)	1	18	6	24
		GFT505-111-7 (Part 3)	1	27	9	36
	Dyslipidaemia/ hyperlipidaemia	**Total**		**87**	**44**	**131**
		GFT505-208-3	2a	63	31	94
		GFT505-207-1	2a	24	13	37
Special population/ Healthy participants	**Renal impairment**	GFT505-118-13	1	**13**	**0**	**13**
	Hepatic impairment	GFT505-118-14	1	**20 [f]**	**0**	**20**
	Healthy participants	**Phase I studies [g]**	1	**543**	**143**	**686**
	Elderly participants (≥75 years) [f]	GFT50511916	1	11 [f]	0	11
	QTc interval study	GFT505-113-9 Part 2	1	89	87	176
Total number of participants exposed				**2,588**	**1,188**	**3,745**

DB=double-blind; LTE=long-term extension; NAFLD=non-alcoholic fatty liver disease; NASH=non-alcoholic steatohepatitis; PBC=primary biliary cholangitis; QTc=corrected QT

Data Source: Module 5.3, respective CSRs (data from studies for which an approved CSR was available)

a The DB period of Study GFT505B319-1 has been completed, whereas the LTE is currently ongoing.

b Safety population includes all participants who received 1 dose of study treatment (Long-term endpoint analysis population - Safety Analysis Set). 7 participants in Study GFT505-315-1 were randomised but not treated, and hence are excluded. Study GFT505-315-1 was terminated early due to lack of efficacy.

c Study GFT505e-218-1 included 10 adolescent participants aged ≥12 to ≤17 years.

Study details			Number of participants Treated		
Study indication	**Study ID**	**Phase**	**Elafibranor**	**Placebo**	**Total**

d 17 participants in Study GFT505-219-8 were to receive both elafibranor and placebo, however, not all participants completed both periods of the study: 9 participants received both elafibranor and placebo and are counted just once in the 'Total' column, 4 received only elafibranor and 4 received only placebo.

e In the crossover Study GFT505-210-6, 22 participants received both elafibranor and placebo and are counted just once in the 'Total' column.

f A total of 16 elderly participants were enrolled in the elafibranor clinical development programme. 14 elderly participants received elafibranor including 11 who received a single-dose of elafibranor in the phase I Study GFT50511916, 1 who received a single-dose of elafibranor in the phase I Study GFT50511814 (hepatic impairment), 1 who received multiple daily doses of elafibranor in the phase III Study GFT505315-1 (NASH), and 1 who received multiple daily doses of elafibranor in the phase III Study GFT505319-1 (PBC). In addition, 2 elderly participants received placebo in the phase III Study GFT505319-1 (PBC)...

g Further details on phase I studies are presented in Appendix. Of note, exposure data have also been included for Study CLIN-60190-452; the CSR for this study was finalised on 08 June 2023 (i.e. after the data cut-off of 01 June 2023).

Table 18: Cumulative participant exposure to elafibranor from completed clinical studies by age and sex

Age group	Number of participants		
	Males	**Females**	**Total**
<18 years	10	0	10
18 to 74 years	1,578	986	2,564
≥75	9	5	14
Total	**1,597**	**991**	**2,588**

Table 19: Cumulative participant exposure to elafibranor from completed clinical studies by dose

Elafibranor dose	Number of participants
<80 mg/day	125
80 mg/day	452
100 mg/day	44
120 mg/day	1,824
180 mg/day	53
240 mg/day	19
300 mg/day	62
360 mg/day	9
Total	**2,588**

Table 20: Cumulative participant exposure to elafibranor from completed clinical studies by duration

Mean duration of exposure	Number of participants
<4 weeks	630
4 to 8 weeks	145
12 weeks	90
≥52 weeks	1,723
Total	**2,588**

PBC indication

206 PBC Participants have been treated in the Phase 2 and 3 PBC studies (**Table 21**). Of these, 138 participants have been treated with elafibranor. Additionally, at the time of the data cut-off for the Phase 3 PBC study 319-1 (last patient last visit for the double-blind period, 01 June 2023), 45 participants who received placebo during the double-blind period had received at least 1 dose of elafibranor 80 mg in the open-label long-term extension treatment phase.

Phase 3 study 319-1

In study 319-1, 161 participants were randomised of which 108 received once daily administration of elafibranor 80 mg and 53 received placebo (2:1 randomisation). The common double-blind period was the first 52 weeks; the overall double-blind period was a treatment period of variable length beyond week 52 during which participants continued to receive study treatment until all participants completed their week 52 visit or until a maximum blinded treatment duration of 104 weeks, whichever came first. This implies that at the time of data cut-off (last patient last visit for the double-blind period, 01 June 2023), participants had variable treatment exposure, but all participants had at least 52 weeks of treatment exposure.

Participants with an inadequate response to ursodeoxycholic acid continued to receive ursodeoxycholic acid in combination with the study treatment, while enrolled participants who were unable to tolerate ursodeoxycholic acid received only the study treatment. Following completion of the double-blind period, participants could enter the open-label long-term extension treatment period. At the data cut-off for the study, 138 participants had entered the long-term extension period, of which 45 participants had received placebo during the double-blind period.

At the time of the data cut-off when all study participants had finished the double-blind treatment period, the mean duration of exposure to elafibranor 80 mg and placebo was 66.2 and 62.2 weeks respectively, corresponding to 137.2 and 63.2 person-years of exposure, respectively (**Table 21**). The median exposure was 63.07 weeks for the 108 participants receiving elafibranor 80 mg, and 5 (4.6%) participants had elafibranor exposure for a period between ≥96 to <104 weeks.

Phase 2 study 216-1

In the Phase 2 PBC Study 216-1, a total of 45 participants with PBC received at least one dose of study treatment, of which 15 participants each received once daily administration of elafibranor 80 mg, elafibranor 120 mg, or placebo (1:1:1 randomisation), with a mean total exposure of 85.7 days, 85.1 days, and 85.1 days, respectively (**Table 21**).

Most of the included patients in studies 216-1 and 319-1 were under 65 years of age (109/138= 79.0%;**Table 23**).

Table 21: Exposure in studies with elafibranor in PBC indication

Study Details		**Elafibranor 80 mg**			**Elafibranor 120 mg**			**Placebo**		
Study ID	**Phase**	**N/n**	**Mean exposure (min, max)**	**Person-years**	**N/n**	**Mean exposure (min, max)**	**Person-years**	**N/n**	**Mean exposure (min, max)**	**Person-years**
GFT505B3 19-1	3	108/ 108	66.2 W (1.1, 104.1)	137.2	NA	NA	NA	53	62.2 W (2.3, 106.0)	63.2
GFT505b2 16-1	2	15/1 4 [a]	85.7 D (80, 106) [b]	3.28	15/1 4 [a]	85.1 D (83, 87) [c]	3.26	15/1 5	85.1 D (82, 91)	3.49

N=total number of participants treated; n=number of participants with data; NA=not applicable; D=Days; PBC=primary biliary cholangitis; W=weeks

a Exposure for the study is presented for 'participants with reliable exposure data'; one participant was excluded from each of elafibranor 80 mg (n=14) and 120 mg (n=14) groups.

b Although 15 participants were treated, the date of Visit 5 for 1 participant was incorrectly recorded as 57 days; hence the participant was excluded from the descriptive statistics.

c Although 15 participants were treated, one participant withdrew from the study 1 day after the first study drug intake and is excluded from the descriptive statistics due to a missing date for the participant's last study drug intake.

Note: Exposure in person-years has been calculated manually using the below formula:

- If the mean exposure presented in the CSR was in 'number of weeks', then the Exposure in Person-years = Number of participants with data x ((mean duration of exposure in weeks x 7)/365.25).
- If the mean exposure presented in the CSR was in 'number of days', then Exposure in Person-years = Number of participants with data x (mean duration of exposure in days/365.25).

Table 22*: *Number of participants with exposure to elafibranor from placebo-controlled studies in PBC by duration of exposure

Study	**Duration of exposure (Number of participants)**				
	<4 weeks	**4 to <12 weeks**	**12 to ≤52 weeks**	**>52 weeks**	**Total**
Phase 3 study 319-1 [a]	1	1	31	75	108
Phase 2 study 216-1 [b]	1	4	25	0	30
Total	***2***	***5***	***56***	***75***	***138***

Study	Duration of exposure (Number of participants)				
	<4 weeks	4 to <12 weeks	12 to ≤52 weeks	>52 weeks	Total

PBC=primary biliary cholangitis

a For Study 319-1, only the double-blind period exposure duration is included, using the data cut-off for the Clinical Study Report. Exposure duration (in days) for each participant is calculated as the minimum of (date of last dose, date of death, date of data cut-off, date of last visit during the double-blind period) – first dose date + 1.

b For Study 216-1, exposure duration (in days) for each participant is calculated as the last dose date – first dose date + 1.

Table 23: Number of participants with exposure to elafibranor from placebo-controlled studies in PBC by age group

Study	Age group (Number of participants)		Total
	18 to 64 years	≥65 years	
Phase 3 study 319-1	86	22	108
Phase 2 study 216-1	23	7	30
Total	***109***	***29***	***138***

PBC=primary biliary cholangitis

Other indications

The number of participants enrolled in elafibranor clinical studies across individual indications are presented in **Table 17**. The exposed populations in the phase 2/3 clinical studies in indications other than PBC include participants with NASH, NAFLD, obesity/overweight and/or abnormal glucose tolerance, diabetes mellitus, and dyslipidaemia/hyperlipidaemia. In addition to the healthy participants, special populations exposed in the phase I clinical studies include participants with renal impairment, hepatic impairment (Child-Pugh [CP] class A, B or C), and elderly participants.

Elafibranor 120 mg is the highest dose evaluated in any clinical indication (Phase 2 or 3 studies), whereas the highest dose evaluated in healthy participants was 360 mg in Phase 1 study GFT505-1139 Part 1. A total of 450 participants have received the clinically relevant dose of 80 mg in the elafibranor clinical development programme including the PBC indication.

2.6.8.2. Adverse events

Below, an overview of the reported treatment-emergent adverse events in the double-blind treatment period in Phase 3 study 319-1 and Phase 2 study 216-1 is presented. The safety analyses set for both studies included all participants who received at least one dose of study treatment.

Phase 3 PBC study 319-1

Table 24 presents a summary of the treatment-emergent adverse events in the safety analysis set. Treatment-emergent adverse events were reported for 104 (96.3%) participants in the elafibranor group and 48 (90.6%) participants in the placebo group. Most treatment-emergent adverse events were mild or moderate in intensity. No differences between treatment groups in treatment-related treatment-emergent adverse events, as assessed by the investigator, were observed (42 [38.9%] and 21 [39.6%] participants in the elafibranor and placebo groups, respectively).

Serious treatment-emergent adverse events were reported for 11 (10.2%) participants in the elafibranor group and 7 (13.2%) participants in the placebo group. Related serious treatment-emergent adverse events were reported for 3 (2.8%) participants in the elafibranor group and 1 (1.9%) participant in the placebo group. Two participants experienced serious treatment-emergent adverse events that led to death; both participants were in the elafibranor group, and all fatal serious treatment-emergent adverse events were considered unrelated to study treatment.

Treatment-emergent adverse events leading to treatment discontinuation were reported for 11 (10.2%) participants in the elafibranor group and 5 (9.4%) participants in the placebo group. Treatment-related treatment-emergent adverse events resulting in treatment discontinuation were reported for 9 (8.3%) participants in the elafibranor group and 4 (7.5%) participants in the placebo group.

A total of 32 (29.6%) participants in the elafibranor group and 14 (26.4%) participants in the placebo group experienced at least one adverse event of special interest. A total of 5 (4.6%) participants and 1 (1.9%) participant in the elafibranor and placebo groups, respectively, had serious adverse events of special interest.

Table 24: Phase 3 PBC study 319-1: overall summary of adverse events (safety analysis set)

	Elafibranor 80 mg (N= 108)		**Placebo (N=53)**	
	n (%) [Events]	**EAIR**	**n (%) [Events]**	**EAIR**
TEAEs	104 (96.3) [626]	4.080	48 (90.6) [259]	3.123
TEAEs by maximum severity				
Mild	40 (37.0) [154]	NA	17 (32.1) [54]	NA
Moderate	53 (49.1) [142]	NA	25 (47.2) [56]	NA
Severe	11 (10.2) [30]	NA	6 (11.3) [8]	NA
TEAEs related to study medication	42 (38.9) [89]	0.420	21 (39.6) [30]	0.440
AESIs	32 (29.6) [41]	0.262	14 (26.4) [15]	0.246
Serious TEAEs	11 (10.2) [30]	0.083	7 (13.2) [10]	0.113
Serious TEAEs related to study medication	3 (2.8) [7]	0.022	1 (1.9) [1]	0.016
TEAEs leading to treatment discontinuation	11 (10.2) [24]	0.080	5 (9.4) [8]	0.078

	Elafibranor 80 mg (N= 108)		**Placebo (N=53)**	
	n (%) [Events]	**EAIR**	**n (%) [Events]**	**EAIR**
TEAEs related to study medication leading to treatment discontinuation	9 (8.3) [13]	0.065	4 (7.5) [4]	0.062
Serious TEAEs leading to treatment discontinuation	3 (2.8) [7]	0.022	1 (1.9) [1]	0.016
Serious TEAEs related to study medication leading to treatment discontinuation	2 (1.9) [2]	0.014	1 (1.9) [1]	0.016
Serious TEAEs leading to death	2 (1.9) [3]	0.014	0 (0.0) [0]	0
Serious TEAEs related to study medication leading to death	0 (0.0) [0]	0	0 (0.0) [0]	0

AESI=adverse event of special interest; CI=confidence interval; EAIR=exposure-adjusted incidence rates (participants per patient-years); NA=not applicable; PBC=primary biliary cholangitis; TEAE=treatment-emergent adverse event

Phase 2 PBC study 216-1

The adverse events that were reported in study 216-1 are summarized in **Table 25**.

A higher proportion of participants treated with elafibranor 120 mg reported overall treatment-emergent adverse events and treatment-related treatment-emergent adverse events (86.7% and 33.3% respectively) compared with those treated with elafibranor 80 mg (80.0% and 13.3%, respectively) and placebo (80.0% and 6.7%, respectively). No difference was observed in the proportion of participants reporting severe treatment-emergent adverse events in any treatment group (2 [13.3%] participants each). Serious treatment-emergent adverse events were reported only in the elafibranor 120 mg group by 2 (13.3%) participants, of which the serious event in one participant was assessed as treatment-related, and in the second participant (unrelated) led to discontinuation of study treatment. There were no treatment-emergent adverse events with a fatal outcome reported in the study. Although adverse events of special interest were not prospectively defined in the study, the sponsor evaluated all reported treatment-emergent adverse events to identify events consistent with treatment-emergent adverse events per the predefined criteria set in the Phase 3 PBC study 319-1.

Table 25: Phase 2 PBC study 216-1: overall summary of adverse events (safety analysis set)

Adverse event category	Elafibranor 80 mg (N=15) n (%) [Events]	Elafibranor 120 mg (N=15) n (%) [Events]	Placebo (N=15) n (%) [Events]
Any TEAE	12 (80.0) [41]	13 (86.7) [47]	12 (80.0) [25]
TEAEs by severity			

Adverse event category	Elafibranor 80 mg (N=15) n (%) [Events]	Elafibranor 120 mg (N=15) n (%) [Events]	Placebo (N=15) n (%) [Events]
Mild	9 (60.0) [35]	9 (60.0) [36]	6 (40.0) [17]
Moderate	1 (6.7) [3]	2 (13.3) [6]	4 (26.7) [6]
Severe	2 (13.3) [3]	2 (13.3) [5]	2 (13.3) [2]
TEAEs related to study medication [a]	2 (13.3) [6]	5 (33.3) [5]	1 (6.7) [1]
Serious TEAE	0 [0]	2 (13.3) [3]	0 [0]
Serious TEAEs related to study medication	0 [0]	1 (6.7) [1]	0 [0]
TEAEs leading to study treatment discontinuation	0 [0]	1 (6.7) [2]	0 [0]
Deaths	0 [0]	0 [0]	0 [0]

AE=adverse event; PBC=primary biliary cholangitis; TEAE=treatment-emergent adverse event
Notes: If severity was missing, then severity was derived as severe. If relationship to study drug for a TEAE was missing, then relationship to study drug was derived as treatment related.
a Included all TEAEs that were "related" and "possibly related." Excluded TEAEs in which the relationship was "unlikely related" or "not related."

2.6.8.2.1. Most frequently reported treatment-emergent adverse events

Phase 3 PBC study 319-1

The most frequently reported treatment-emergent adverse events in ≥2% of participants in any treatment group, the corresponding exposure-adjusted incidence rate (EAIR), and EAIR difference are presented in **Table 26** by system organ class and preferred term. In both treatment groups, (elafibranor versus placebo), the most commonly reported treatment-emergent adverse events were in the system organ classes of infections and infestations (63.0% versus 58.5%) and gastrointestinal disorders (50.9% versus 30.2%).

Treatment-emergent adverse events reported in ≥5% of participants in the elafibranor group and with a higher incidence than the placebo group (difference >1%) were mostly gastrointestinal in nature and transient, including vomiting (11.1% versus 1.9%), diarrhoea (11.1% versus 9.4%), nausea (11.1% versus 5.7%), constipation (8.3% versus 1.9%), abdominal pain upper (7.4% versus 5.7%), and gastrooesophageal reflux disease (6.5% versus 1.9%). The other events were arthralgia (8.3% versus 3.8%) and upper respiratory tract infection (6.5% versus 3.8%). The corresponding EAIRs for these events were generally similar between the two treatment groups. The only preferred term with a ≥5% higher incidence in the elafibranor group compared with the placebo group and with a 95% CI for EAIR difference that did not include 0 was vomiting (95% CI: [0.015; 0.139]).

Of note, participants treated with elafibranor experienced fewer treatment-emergent adverse events of pruritus and fatigue compared with placebo (20.4% versus 26.4% for pruritus and 9.3% versus 13.2% for fatigue, respectively). Other treatment-emergent adverse events reported in ≥5% of participants in the elafibranor group with lower incidence than in the placebo group were COVID-19 (28.7% in the

elafibranor group versus 37.7% in the placebo group), urinary tract infection (11.1% versus 18.9%), and headache (8.3% versus 11.3%).

Of the headache events, 3.7% in the elafibranor group and 1.9% in placebo group were assessed as related by the investigator. In 4 of the 9 participants with headache in the elafibranor group, the event occurred within 10 days of initiation of treatment. The events of headache were mild to moderate in severity, and most resolved within a week without the need for interruption of elafibranor treatment.

Table 26: Phase 3 PBC study 319-1: summary of treatment-emergent adverse events by system organ class and preferred term occurring in ≥2% of participants in either treatment group (safety analysis set)

	Elafibranor 80 mg (N= 108)			**Placebo (N=53)**		
System organ class Preferred term	**n (%)**	**Events**	**EAIR**	**n (%)**	**Events**	**EAIR**
Any TEAEs	**104 (96.3)**	**626**	**4.08**	**48 (90.6)**	**259**	**3.123**
Infections and infestations	**68 (63.0)**	**123**	**0.838**	**31 (58.5)**	**51**	**0.735**
COVID-19	31 (28.7)	31	0.263	20 (37.7)	20	0.402
Urinary tract infection	12 (11.1)	16	0.093	10 (18.9)	11	0.169
Upper respiratory tract infection	7 (6.5)	8	0.052	2 (3.8)	2	0.032
Sinusitis	5 (4.6)	5	0.037	2 (3.8)	2	0.031
Gastroenteritis	4 (3.7)	5	0.03	1 (1.9)	2	0.016
Nasopharyngitis	4 (3.7)	5	0.029	1 (1.9)	1	0.016
Influenza	4 (3.7)	4	0.029	1 (1.9)	1	0.016
Herpes zoster	3 (2.8)	4	0.022	0	0	0
Bacteriuria	3 (2.8)	3	0.022	0	0	0
Pneumonia	3 (2.8)	3	0.022	0	0	0
Skin infection	0	0	0	2 (3.8)	2	0.032
Gastrointestinal disorders	**55 (50.9)**	**124**	**0.648**	**16 (30.2)**	**32**	**0.335**
Vomiting	12 (11.1)	15	0.092	1 (1.9)	1	0.016
Diarrhoea	12 (11.1)	13	0.094	5 (9.4)	5	0.083
Nausea	12 (11.1)	13	0.096	3 (5.7)	3	0.048
Constipation	9 (8.3)	11	0.069	1 (1.9)	1	0.016
Abdominal pain upper	8 (7.4)	10	0.061	3 (5.7)	5	0.049
Gastrooesophageal reflux disease	7 (6.5)	7	0.053	1 (1.9)	1	0.016
Dry mouth	5 (4.6)	5	0.038	1 (1.9)	1	0.016
Abdominal pain	4 (3.7)	5	0.029	0	0	0
Dyspepsia	4 (3.7)	4	0.029	3 (5.7)	3	0.048
Abdominal distension	3 (2.8)	4	0.022	0	0	0
Flatulence	3 (2.8)	3	0.022	0	0	0
Abdominal discomfort	0	0	0	2 (3.8)	2	0.032
Musculoskeletal and connective tissue disorders	**34 (31.5)**	**53**	**0.299**	**17 (32.1)**	**29**	**0.347**
Arthralgia	9 (8.3)	12	0.068	2 (3.8)	2	0.031
Osteoporosis	5 (4.6)	5	0.036	1 (1.9)	1	0.016
Back pain	4 (3.7)	5	0.03	6 (11.3)	6	0.102
Pain in extremity	3 (2.8)	5	0.022	3 (5.7)	4	0.049
Muscle spasms	3 (2.8)	3	0.022	3 (5.7)	4	0.049
Myalgia	3 (2.8)	3	0.022	0	0	0
Osteoarthritis	3 (2.8)	3	0.022	0	0	0
Skin and subcutaneous tissue disorders	**33 (30.6)**	**47**	**0.304**	**20 (37.7)**	**25**	**0.375**
Pruritus	22 (20.4)	26	0.18	14 (26.4)	14	0.244
Alopecia	3 (2.8)	3	0.022	2 (3.8)	2	0.032
Hyperhidrosis	3 (2.8)	3	0.022	0	0	0
Rash	3 (2.8)	3	0.022	1 (1.9)	1	0.016
Skin lesion	3 (2.8)	3	0.022	2 (3.8)	2	0.031
Metabolism and nutrition disorders	**33 (30.6)**	**42**	**0.277**	**12 (22.6)**	**17**	**0.209**

	Elafibranor 80 mg (N= 108)			Placebo (N=53)		
System organ class Preferred term	**n (%)**	**Events**	**EAIR**	**n (%)**	**Events**	**EAIR**
Abnormal weight gain	21 (19.4)	21	0.164	10 (18.9)	11	0.168
Abnormal loss of weight	5 (4.6)	5	0.037	0	0	0
Decreased appetite	3 (2.8)	3	0.022	1 (1.9)	1	0.016
Iron deficiency	3 (2.8)	3	0.022	0	0	0
Vitamin D deficiency	2 (1.9)	2	0.014	2 (3.8)	2	0.032
Investigations	**29 (26.9)**	**43**	**0.237**	**9 (17.0)**	**18**	**0.161**
Blood creatine phosphokinase increased	4 (3.7)	4	0.029	0	0	0
Weight increased	4 (3.7)	4	0.029	1 (1.9)	1	0.016
Blood bilirubin increased	3 (2.8)	3	0.022	1 (1.9)	1	0.016
Lipase increased	1 (0.9)	2	0.007	2 (3.8)	2	0.033
General disorders and administration site conditions	**26 (24.1)**	**34**	**0.219**	**13 (24.5)**	**19**	**0.233**
Fatigue	10 (9.3)	10	0.077	7 (13.2)	8	0.114
Influenza like illness	4 (3.7)	5	0.029	1 (1.9)	1	0.016
Oedema peripheral	4 (3.7)	5	0.029	2 (3.8)	2	0.032
Pain	0	0	0	4 (7.5)	4	0.065
Nervous system disorders	**24 (22.2)**	**28**	**0.199**	**15 (28.3)**	**17**	**0.285**
Headache	9 (8.3)	9	0.067	6 (11.3)	6	0.098
Dizziness	4 (3.7)	4	0.03	1 (1.9)	1	0.016
Injury, poisoning and procedural complications	**21 (19.4)**	**28**	**0.171**	**9 (17.0)**	**10**	**0.155**
Fall	5 (4.6)	5	0.037	2 (3.8)	2	0.032
Ligament sprain	3 (2.8)	3	0.022	0	0	0
Tooth fracture	1 (0.9)	1	0.007	2 (3.8)	2	0.032
Respiratory, thoracic and mediastinal disorders	**14 (13.0)**	**21**	**0.105**	**6 (11.3)**	**8**	**0.102**
Oropharyngeal pain	4 (3.7)	4	0.029	0	0	0
Cough	3 (2.8)	3	0.022	2 (3.8)	2	0.031
Dyspnoea	2 (1.9)	2	0.014	2 (3.8)	2	0.032
Renal and urinary disorders	**12 (11.1)**	**15**	**0.089**	**1 (1.9)**	**2**	**0.016**
Acute kidney injury	3 (2.8)	3	0.022	1 (1.9)	1	0.016
Blood and lymphatic system disorders	**8 (7.4)**	**9**	**0.06**	**3 (5.7)**	**4**	**0.048**
Anaemia	3 (2.8)	4	0.022	1 (1.9)	1	0.016
Lymphadenopathy	3 (2.8)	3	0.022	1 (1.9)	2	0.016
Hepatobiliary disorders	**8 (7.4)**	**9**	**0.059**	**1 (1.9)**	**1**	**0.016**
Cholelithiasis	3 (2.8)	3	0.022	0	0	0
Vascular disorders	**8 (7.4)**	**8**	**0.06**	**3 (5.7)**	**3**	**0.047**
Hypertension	4 (3.7)	4	0.029	3 (5.7)	3	0.047
Psychiatric disorders	**7 (6.5)**	**9**	**0.052**	**6 (11.3)**	**7**	**0.099**
Depression	4 (3.7)	4	0.03	2 (3.8)	2	0.032
Insomnia	1 (0.9)	1	0.007	2 (3.8)	2	0.031
Cardiac disorders	**5 (4.6)**	**7**	**0.036**	**3 (5.7)**	**3**	**0.049**
Palpitations	3 (2.8)	3	0.022	2 (3.8)	2	0.032
Eye disorders	**5 (4.6)**	**5**	**0.037**	**6 (11.3)**	**6**	**0.097**
Cataract	0	0	0	2 (3.8)	2	0.031

CI=confidence interval; EAIR=exposure-adjusted incidence rates (participants per patient-years); PBC=primary biliary cholangitis; TEAE=treatment-emergent adverse event
Data Source: Study 319-1

Treatment-emergent adverse events in the open-label long-term extension period of Phase 3 PBC study 319-1

In study 319-1, at the data cut-off for the study (last patient last visit for the double-blind period), 138 participants had entered the long-term extension period in which all participants received elafibranor 80 mg once daily, of which 45 participants had received placebo during the double-blind treatment period.

Two participants (one in the prior elafibranor group, and one in the prior placebo group) had serious treatment-emergent adverse events. A participant in the prior elafibranor group had a serious treatment-emergent adverse event of autoimmune hepatitis of moderate intensity; this event was not related to the study drug but led to the participant's withdrawal from treatment. A participant in the prior placebo group had serious treatment-emergent adverse events of bile duct stone and cholecystitis, which were severe in intensity and not related to the study drug; the study drug was interrupted for these events.

Until the data cut-off, no other participants had serious treatment-emergent adverse events, adverse events of special interest, or treatment-emergent adverse events leading to study drug discontinuation during the long-term extension period.

Phase 2 PBC study 216-1

In study 216-1, the most frequently reported treatment-emergent adverse events (in ≥1 participant in any treatment group) were in the system organ classes of gastrointestinal disorders (6.7%, 53.3%, and 33.3% in the elafibranor 80 mg once daily, elafibranor 120 mg once daily, and placebo once daily groups, respectively); infection and infestations (40.0%, 20.0%, and 20.0%, respectively); nervous system disorders (40.0%, 20.0%, and 13.3%, respectively); general disorders and administration site conditions (26.7%, 26.7%, and 0%, respectively); and skin and subcutaneous tissue disorders (26.7%, 20.0%, and 20.0%, respectively).

The most frequently reported treatment-emergent adverse events occurring in 2 or more participants on elafibranor 80 mg and at a higher frequency than placebo were viral upper respiratory tract infection, dizziness, headache, and pruritus.

Table 27: Phase 2 PBC study 216-1: summary of treatment-emergent adverse events reported in ≥1 participant in any treatment group by system organ class and preferred term (safety analysis set)

System organ class **Preferred term**	**Elafibranor 80 mg (N=15) n (%) [Events]**	**Elafibranor 120 mg (N=15) n (%) [Events]**	**Placebo (N=15) n (%) [Events]**
Any TEAE	**12 (80.0) [41]**	**13 (86.7) [47]**	**12 (80.0) [25]**
Gastrointestinal disorders	**1 (6.7) [1]**	**8 (53.3) [10]**	**5 (33.3) [7]**
Diarrhoea	0 [0]	2 (13.3) [2]	2 (13.3) [2]
Nausea	0 [0]	3 (20.0) [3]	1 (6.7) [1]
General disorders and administration site conditions	**4 (26.7) [4]**	**4 (26.7) [4]**	**0 [0]**
Fatigue	1 (6.7) [1]	3 (20.0) [3]	0 [0]
Infections and infestations	**6 (40.0) [8]**	**3 (20.0) [5]**	**3 (20.0) [4]**
Urinary tract infection	1 (6.7) [1]	3 (20.0) [3]	0 [0]
Viral upper respiratory tract infection	3 (20.0) [3]	0 [0]	2 (13.3) [2]
Nervous system disorders	**6 (40.0) [7]**	**3 (20.0) [5]**	**2 (13.3) [2]**
Dizziness	2 (13.3) [2]	0 [0]	1 (6.7) [1]
Headache	2 (13.3) [3]	2 (13.3) [2]	1 (6.7) [1]
Skin and subcutaneous tissue disorders	**4 (26.7) [5]**	**3 (20.0) [3]**	**3 (20.0) [4]**
Pruritus	3 (20.0) [3]	3 (20.0) [3]	2 (13.3) [3]

PBC=primary biliary cholangitis; PT=preferred term; SOC=system organ class; TEAE=treatmentemergent adverse event

System organ class Preferred term	Elafibranor 80 mg (N=15) n (%) [Events]	Elafibranor 120 mg (N=15) n (%) [Events]	Placebo (N=15) n (%) [Events]

Note: Participants with multiple TEAEs within the same SOC and/or PT were only counted once within the respective frequencies.
Data Source: Study 216-1

Adverse drug reactions

In Phase 3 PBC study 319-1 and Phase 2 PBC study 216-1, the investigators assessed whether the observed treatment-emergent adverse events were study treatment-related. In both studies, the investigator's assessment was not reviewed by a centralized safety monitoring committee.

Phase 3 PBC study 319-1

Related treatment-emergent adverse events reported for ≥1% of participants in either treatment group are shown in **Table 28**. Treatment-related treatment-emergent adverse events were reported for 42 (38.9%) participants in the elafibranor group and 21 (39.6%) participants in the placebo group. In the elafibranor group, the related treatment-emergent adverse events with the highest incidence were pruritus (8.3% versus 11.3% in the placebo group) and nausea (7.4% versus 1.9% in the placebo group). The only treatment-related treatment-emergent adverse event reported in ≥5% of participants in the elafibranor group and with a higher incidence than the placebo group (difference >1%) was nausea (7.4% versus 1.9%).

Table 28: Phase 3 PBC study 319-1: treatment-emergent adverse events related to study medication reported for ≥1% of participants in either treatment group (safety analysis set)

	Elafibranor 80 mg (N=108)		Placebo (N=53)	
System organ class Preferred term	**n (%) [Events]**	**EAIR**	**n (%) [Events]**	**EAIR**
Any treatment-related TEAEs	**42 (38.9) [89]**	**0.42**	**21 (39.6) [30]**	**0.44**
Gastrointestinal disorders	**23 (21.3) [34]**	**0.199**	**9 (17.0) [11]**	**0.162**
Nausea	8 (7.4) [8]	0.061	1 (1.9) [1]	0.016
Constipation	4 (3.7) [4]	0.03	1 (1.9) [1]	0.016
Dry mouth	3 (2.8) [3]	0.022	1 (1.9) [1]	0.016
Gastrooesophageal reflux disease	3 (2.8) [3]	0.022	1 (1.9) [1]	0.016
Abdominal pain upper	2 (1.9) [2]	0.015	2 (3.8) [2]	0.032
Flatulence	2 (1.9) [2]	0.015	0	0
Frequent bowel movements	2 (1.9) [2]	0.015	0	0
Diarrhoea	1 (0.9) [1]	0.007	3 (5.7) [3]	0.048
Dyspepsia	1 (0.9) [1]	0.007	2 (3.8) [2]	0.031
Skin and subcutaneous tissue disorders	**11 (10.2) [13]**	**0.085**	**7 (13.2) [7]**	**0.117**
Pruritus	9 (8.3) [9]	0.068	6 (11.3) [6]	0.098
Nervous system disorders	**8 (7.4) [9]**	**0.06**	**2 (3.8) [2]**	**0.032**
Headache	4 (3.7) [4]	0.029	1 (1.9) [1]	0.016

	Elafibranor 80 mg (N=108)		Placebo (N=53)	
System organ class Preferred term	**n (%) [Events]**	**EAIR**	**n (%) [Events]**	**EAIR**
Dizziness	2 (1.9) [2]	0.014	0	0
Investigations	**7 (6.5) [12]**	**0.051**	**3 (5.7) [3]**	**0.048**
Blood creatine phosphokinase increased	3 (2.8) [3]	0.022	0	0
General disorders and administration site conditions	**5 (4.6) [5]**	**0.037**	**3 (5.7) [3]**	**0.048**
Fatigue	4 (3.7) [4]	0.029	2 (3.8) [2]	0.031
Metabolism and nutrition disorders	**4 (3.7) [4]**	**0.029**	**1 (1.9) [1]**	**0.016**
Abnormal weight gain	2 (1.9) [2]	0.014	1 (1.9) [1]	0.016
Musculoskeletal and connective tissue disorders	**4 (3.7) [4]**	**0.029**	**1 (1.9) [1]**	**0.016**
Myalgia	2 (1.9) [2]	0.015	0	0

EAIR=exposure-adjusted incidence rates (participants per patient-years); PBC=primary biliary cholangitis; TEAE=treatment-emergent adverse event
Data Source: Study 319-1

Phase 2 PBC study 216-1

In study 216-1, treatment-related treatment-emergent adverse events were reported in a higher proportion of participants treated with elafibranor 120 mg (33.3%) compared with elafibranor 80 mg (13.3%) or placebo (6.7%). The only related treatment-emergent adverse event that was reported in >1 participant in any treatment group was nausea, experienced by 3 (20.0%) participants in the elafibranor 120 mg group (**Table 29**). No events of nausea were considered related in the elafibranor 80 mg or placebo group.

Except for the participant (elafibranor 120 mg group) with a related treatment-emergent adverse event of autoimmune hepatitis, which was severe and serious, all other related treatment-emergent adverse events were mild or moderate in intensity, and none of the related treatment-emergent adverse events led to study treatment discontinuation.

Table 29: Phase 2 PBC study 216-1: summary of treatment-related treatment-emergent adverse events reported by preferred term (safety analysis set)

Preferred Term	Elafibranor 80 mg (N=15) n (%) [Events]	Elafibranor 120 mg (N=15) n (%) [Events]	Placebo (N=15) n (%) [Events]
Any treatment-related TEAE	**2 (13.3) [6]**	**5 (33.3) [5]**	**1 (6.7) [1]**
Nausea	0 [0]	3 (20.0) [3]	0 [0]
Pruritus	1 (6.7) [1]	1 (6.7) [1]	1 (6.7) [1]
Autoimmune hepatitis	0 [0]	1 (6.7) [1]	0 [0]
Blood bilirubin increased	1 (6.7) [1]	0 [0]	0 [0]
Blood cholesterol increased	1 (6.7) [1]	0 [0]	0 [0]
Dizziness	1 (6.7) [1]	0 [0]	0 [0]
Gamma-glutamyl transferase increased	1 (6.7) [1]	0 [0]	0 [0]
Transaminases increased	1 (6.7) [1]	0 [0]	0 [0]

PBC=primary biliary cholangitis; PT=preferred term; TEAE=treatment-emergent adverse event
Data Source: Study 216-1 Note: Participants with multiple TEAEs within the same PT were only counted once within the respective frequencies.

Preliminary safety evaluation in the long-term extension phase of study 319-1

The 4–5-year long-term extension of study 319-1 is ongoing. In this study phase, all study patients are treated with elafibranor 80 mg once daily.

After submission of the marketing authorisation application dossier, safety data that were obtained in the evaluation period from 01 June 2023 until 02 October 2023 were submitted.

At the data cutoff, a total of 153 participants had received at least one dose of elafibranor, including 108 participants who received elafibranor in the double-blind period and 45 participants who had received placebo during the double-blind period and received elafibranor in the long-term extension period. Overall patient years of exposure increased from 137.4 years (N=108) in the double-blind period at the initial data cutoff to 202.3 years (N=153) at the 4-month safety update cutoff (cumulative double-blind + long-term extension periods). The mean exposure to elafibranor of study participants who were treated with elafibranor during the double-blind and long-term extension period increased from 66.4 weeks to 87.2 weeks during the additional evaluation period. In the participants who had received placebo treatment during the double-blind treatment period and who received elafibranor during the long-term extension period, the mean duration of exposure to elafibranor at the 4-month safety update data cutoff was 25.37 weeks (range 0.7 to 49.1 weeks), and a total of 28/45 (62.2%) participants had been exposed to elafibranor for ≥24 to <36 weeks.

An overall summary of the treatment-emergent adverse events at the 4-month safety update data cutoff in Study 319-1 is presented in **Table 30**.

In the elafibranor double-blind plus long-term extension period, the occurrence of any treatment-emergent adverse event (96.3% vs 96.3%), treatment-related treatment-emergent adverse events (39.8% vs 37.0%), serious treatment-emergent adverse events (11.1% vs 10.2%), treatment-related serious treatment-emergent adverse events (2.8% vs 2.8%), treatment-emergent adverse events leading to treatment discontinuation (11.1% vs 10.2%), and treatment-emergent adverse events leading to study discontinuation (5.6% vs 4.6%) at the additional 4-month safety update cut-off and the initial cut-off were comparable. The most frequently reported treatment-emergent adverse events at the 4-month safety update cut-off were in the system organ classes of infections and infestations (66.7%) and gastro-intestinal disorders (52.8%).

Table 30: Overall summary of treatment-emergent adverse events in PBC Phase 3 study 319-1 - Safety update safety analyses set

MAA Data cutoff	MAA Data cutoff (01 June 2023)		4MSU Data cutoff (02 October 2023)					
	DB Period		Elafibranor DB + LTE Periods					
	Elafibranor 80 mg DB (N=108)		Elafibranor 80 mg DB → Elafibranor 80 mg LTE (N=108)		Placebo DB → Elafibranor 80 mg LTE (N=45)		All Elafibranor 80 mg (N=153)	
	n (%) Events	Patient-Years EAIR	n (%) Events	Patient-Years EAIR	n (%) Events	Patient-Years EAIR	n (%) Events	Patient-Years EAIR
TEAEs	104 (96.3) 630	25.5 4.080	104 (96.3) 721	27.3 3.804	20 (44.4) 47	14.6 1.374	124 (81.0) 768	41.9 2.960
TEAEs by maximum severity								
Mild	40 (37.0) 157	ND	36 (33.3) 169	ND	11 (24.4) 20	ND	47 (30.7) 189	ND
Moderate	53 (49.1) 142	ND	56 (51.9) 162	ND	8 (17.8) 14	ND	64 (41.8) 176	ND
Severe	11 (10.2) 31	ND	12 (11.1) 36	ND	1 (2.2) 2	ND	13 (8.5) 38	ND

MAA Data cutoff	MAA Data cutoff (01 June 2023)		4MSU Data cutoff (02 October 2023)					
	DB Period		Elafibranor DB + LTE Periods					
	Elafibranor 80 mg DB (N=108)		Elafibranor 80 mg DB → Elafibranor 80 mg LTE (N=108)		Placebo DB → Elafibranor 80 mg LTE (N=45)		All Elafibranor 80 mg (N=153)	
	n (%) Events	Patient-Years EAIR	n (%) Events	Patient-Years EAIR	n (%) Events	Patient-Years EAIR	n (%) Events	Patient-Years EAIR
TEAEs related to study medication	40 (37.0) 90	99.7 0.401	43 (39.8) 97	128.0 0.336	5 (11.1) 13	20.2 0.247	48 (31.4) 110	148.2 0.324
Serious TEAEs	11 (10.2) 31	132.3 0.083	12 (11.1) 36	172.6 0.070	2 (4.4) 4	21.3 0.094	14 (9.2) 40	193.9 0.072
Serious TEAEs related to study medication	3 (2.8) 7	137.8 0.022	3 (2.8) 7	180.8 0.017	0 (0.0) 0	22.0 0	3 (2.0) 7	202.7 0.015
TEAEs leading to treatment discontinuation	11 (10.2) 24	136.9 0.080	12 (11.1) 25	179.7 0.067	0 (0.0) 0	22.0 0	12 (7.8) 25	201.7 0.059
TEAEs leading to study discontinuation	5 (4.6) 6	138.3 0.036	6 (5.6) 7	181.2 0.033	0 (0.0) 0	22.0 0	6 (3.9) 7	203.1 0.030
TEAEs related to study medication leading to treatment discontinuation	9 (8.3) 13	137.3 0.066	9 (8.3) 13	180.2 0.050	0 (0.0) 0	22.0 0	9 (5.9) 13	202.2 0.045
TEAEs related to study medication leading to study discontinuation	4 (3.7) 4	138.4 0.029	4 (3.7) 4	181.4 0.022	0 (0.0) 0	22.0 0	4 (2.6) 4	203.4 0.020
Serious TEAEs leading to treatment discontinuation	3 (2.8) 7	137.9 0.022	4 (3.7) 8	180.8 0.022	0 (0.0) 0	22.0 0	4 (2.6) 8	202.7 0.020
Serious TEAEs related to study medication leading to treatment discontinuation	2 (1.9) 2	138.1 0.014	2 (1.9) 2	181.1 0.011	0 (0.0) 0	22.0 0	2 (1.3) 2	203.0 0.010
Serious TEAEs leading to study discontinuation	2 (1.9) 2	138.7 0.014	3 (2.8) 3	181.5 0.017	0 (0.0) 0	22.0 0	3 (2.0) 3	203.5 0.015
Serious TEAEs related to study medication leading to study discontinuation	1 (0.9) 1	138.8 0.007	1 (0.9) 1	181.8 0.006	0 (0.0) 0	22.0 0	1 (0.7) 1	203.7 0.005
Serious TEAEs leading to death	2 (1.9) 3	138.7 0.014	2 (1.9) 3	181.7 0.011	0 (0.0) 0	22.0 0	2 (1.3) 3	203.6 0.010
Serious TEAEs related to study medication leading to death	0 (0.0) 0	138.8 0	0 (0.0) 0	181.8 0	0 (0.0) 0	22.0 0	0 (0.0) 0	203.7 0
TEAEs related to study procedure	5 (4.6) 5	136.0 0.037	6 (5.6) 6	177.0 0.034	0 (0.0) 0	22.0 0	6 (3.9) 6	199.0 0.030

AE=adverse event; DB=double-blind; EAIR=exposure-adjusted incidence rates (patients per patient-year); LTE=long-term extension; 4MSU=4-Month Safety Update; MAA=Marketing Authorisation Application; SAP=statistical analysis plan; TEAE=treatment-emergent adverse event.
Data Source: 4MSU

With respect to study 319-1, only the safety data that were obtained during the double-blind treatment period will be discussed in this overview, since the long-term extension phase of this study is still ongoing.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

Phase 3 PBC study 319-1

Serious treatment-emergent adverse events were reported for 11 (10.2%) participants in the elafibranor group and 7 (13.2%) participants in the placebo group. Serious treatment-emergent adverse events reported for >1 participant in the elafibranor group were acute kidney injury (3 participants, 2.8%) and hip fracture (2 participants, 1.9%). The events of acute kidney injury are discussed above. The events of hip fracture were both due to falls, with 1 participant having a medical

history of osteoporosis and bone mineral density reporting a T-score of 2.7 at baseline; and the other participant having a relevant medical history and evidence of osteopenia with bone mineral density reporting at T score of 1.1 at baseline. No other serious treatment-emergent adverse events were reported for >1 participant in either of the treatment groups, and no trend was observed.

Three (2.8%) elafibranor-treated participants and 1 (1.9%) placebo-treated participant had serious treatment-emergent adverse events considered related to the study medication. In the elafibranor group, the related serious treatment-emergent adverse events were moderate and severe ascites, moderate acute kidney injury, and severe rhabdomyolysis in 1 participant; moderate Crohn's disease and severe sudden hearing loss in 1 participant; and moderate tremor and mild parkinsonism in 1 participant. All these participants were withdrawn from study drug. In the placebo participant, the related serious treatment-emergent adverse event was severe cataract and also led to study drug withdrawal.

Phase 2 PBC study 216-1
Serious treatment-emergent adverse events were reported only in the elafibranor 120 mg group by 2 (13.3%) participants: 1 participant experienced autoimmune hepatitis (possibly related) and 1 participant experienced serious treatment-emergent adverse events of ischemic stroke (not related) and post procedural stroke (not related), which occurred within 24 hours of first study treatment intake and also led to permanent discontinuation of study treatment.

Deaths

Phase 3 PBC study 319-1
Two deaths (two 60-65-year female study patients) due to serious treatment-emergent adverse events were reported in the elafibranor group. The fatal serious treatment-emergent adverse events were multiple organ dysfunction syndrome in one participant and biliary sepsis and acute kidney injury in the other participant. None of these events were considered related to the study treatment. One patient died after 30 days from elective surgery for abdominal hernia, and the cause of death was considered related to post-surgical complications. The other patient had relevant medical history. The death occurred following biliary sepsis and acute kidney injury, assessed as not related to the study treatment. No deaths were reported in placebo-treated study patients.

Phase 2 PBC study 216-1
There were no treatment-emergent adverse events with a fatal outcome reported in any treatment group during study 2161.

Other significant events

Malignancies
Seven (6.5%) participants in the elafibranor group and 3 (5.7%) participants in the placebo group had treatment-emergent adverse events in the system organ class of neoplasms benign, malignant and unspecified (including cysts and polyps) in study 319-1. None of these events were considered related to the study drug or resulted in study drug discontinuation.

CPK elevations
Four (3.7%) participants in the elafibranor group (and none in the placebo group) had 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. No clear trend was observed in time to onset of these events (range: 29-288 days). In 2 of the 4 cases, the CPK was >5 x

ULN. One case was associated to renal injury (probably as consequence of muscle injury). In all cases, the participants had concomitant disease (autoimmune thyroiditis, chronic kidney disease) or concomitant medications (statins) known to be associated with CPK elevations.

Renal injury
In study 319-1, three (2.8%) participants in the elafibranor group and 1 (1.9%) participant in the placebo group had renal injury (all these events were serious). An elafibranor participant with moderate event of acute kidney injury had rhabdomyolysis. In the second participant in the active treatment arm, the acute kidney injury was concurrent with biliary sepsis and multi-system involvement and was considered contributory to the fatal outcome. In the third participant, the acute renal failure occurred in the setting of postoperative multiorgan failure which also had a fatal outcome (and was considered unrelated to the study drug). Two of the events occurred in the setting of a complex clinical condition of systemic involvement and deterioration leading to death, and in both of those cases, the acute kidney injury was considered unrelated to the study drug. The other acute kidney injury event occurred in the context of rhabdomyolysis and assessed as possibly related to the study drug.

Central nervous system
Overall, nervous system disorders were slightly less frequent in elafibranor than placebo (22.2% vs 28.3%) in study 319-1.
One (0.9%) participant in the elafibranor group experienced a serious treatment-emergent adverse event of moderate tremor that led to study drug discontinuation. This participant also experienced a serious treatment-emergent adverse event of parkinsonism. A consulting neurologist indicated a rest tremor may have been present already prior to study drug initiation. Both the tremor and the parkinsonism were assessed as related to the study drug by the investigator.

2.6.8.4. Laboratory findings

The laboratory evaluations and other evaluations that were conducted in study 319-1 are described below. Overall, the observations with respect to laboratory evaluations in Phase 2 study 216-1 are in line with those in study 319-1.

Haematology parameters
No clinically relevant differences between treatment groups were noted for any haematologic values over time or in potentially clinically significant abnormalities values.

In study 319-1, there were 2 (1.9%) participants in the elafibranor group with elevated international normalized ratio (INR) ≥1.5 x upper limit of normal versus none in the placebo group. It was explained that the observed INR elevations was a chance finding in one participant and was due to apixaban treatment for paroxysmal atrial fibrillation in another participant. In both cases the observed INR elevations were considered unrelated to elafibranor treatment.

Chemistry parameters
Chemistry parameters of interest (creatine phosphokinase and hepatic, renal, and lipid parameters) are discussed separately below. Overall, there were no clinically meaningful changes from baseline or notable trends in either the elafibranor or placebo treatment group in study 319-1.

Creatine phosphokinase (CPK)
At baseline, the mean (SD) values for CPK were similar in the elafibranor group and the placebo group (78.7 [46.4] U/l and 79.2 [52.5] U/l, respectively). These values were within normal limits (26 to

192 U/l). At week 52, the observed mean values remained within normal limits (82.2 [51.3] U/l and 91.1 [102.7] U/l, respectively). The mean change from baseline at week 52 was 6.2 (38.1) U/l in the elafibranor group and 12.3 (67.0) U/l in the placebo group.

Hepatic parameters

Hepatic laboratory parameters of interest are discussed individually below.

Alkaline phosphatase (ALP)

All participants had abnormal, elevated ALP values at baseline. In the laboratory safety data, at week 52, the mean (SD) change from baseline in ALP was 117.7 (96.5) U/l in the elafibranor group and 8.8 (91.2) U/l in the placebo group.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)

At baseline, the mean values for ALT, AST, and GGT were above the normal range in both the elafibranor and placebo groups. Although decreases in all of these parameters were observed over time in both groups, mean values at week 52 remained above normal range.

Total bilirubin (TB)

At baseline, the mean values for TB were within the normal range 0 to 20.5 µmol/l) in both treatment groups. In the laboratory safety data at week 52, the observed mean value was still within normal range for both treatment groups. The mean change from baseline at week 52 was 0.67 (3.18) µmol/l in the elafibranor group and 0.87 (4.29) µmol/l in the placebo group.

Renal parameters

Renal laboratory parameters of interest are discussed individually below.

Serum creatinine

At baseline, mean (SD) values were similar in the elafibranor and placebo groups (65.92 [12.84] µmol/l and 65.61 [11.65] µmol/l, respectively), which were in the normal range (44.2 to 79.6 µmol/l). At week 52, the observed mean value was still within normal range (65.84 [12.18] µmol/l in the elafibranor group and 65.67 [10.56] µmol/l in the placebo group) (**Figure 10**). The mean change from baseline at week 52 was 0.01 (8.03) µmol-/l in the elafibranor group and 0.67 (7.60) µmol/l in the placebo group. In the majority of- participants, increases in serum creatinine levels were often within the normal range and were not associated with increases in cystatin C.

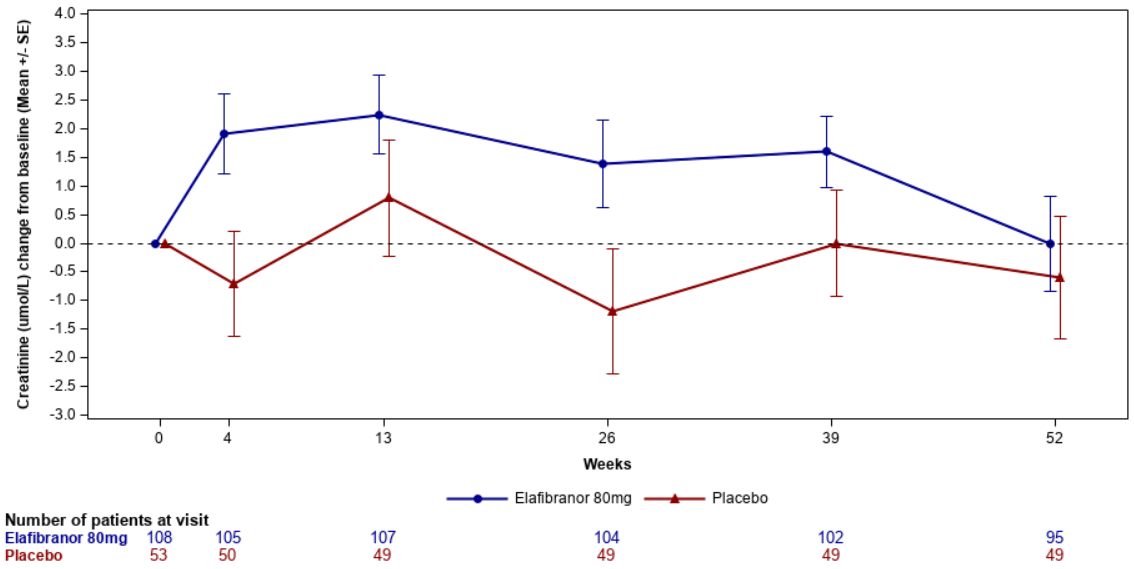


Figure 10: Phase 3 PBC study 319-1: change from baseline in creatinine (µmol/l) (mean +/- SE) over time up to week 52 (Intention-to-treat analysis set)

ITT=intent-to-treat; PBC=primary biliary cholangitis; SE=standard error
Data Source: Study 319-1

The occurrence of at least 1 serum creatinine post-baseline value >ULN for participants whose baseline level of serum creatinine was normal (i.e. <ULN) is summarised in **Table 31**. The number and percentage of participants who had normal baseline serum creatinine values (i.e. ≤ULN) and who had at least 1 occurrence of a post baseline value >ULN was 14/96 (14.6%) participants in the elafibranor group and 3/45 (6.7%) in the placebo group. Of these participants, only 1 (1.0%) in the elafibranor group and none in the placebo group were classified as Kidney Disease Improving Global Outcomes Acute Kidney Injury (KDIGO AKI) stage 1; no participants in either treatment group were classified as AKI stage 2 or stage 3.

The percentage of participants who had baseline serum creatinine values ≤ULN and had a last recorded post baseline value >ULN was 7.3% in the elafibranor group and 2.2% in the placebo group, with 1 (1.0%) participant (elafibranor group) classified as AKI stage 1 and 1 (1.0%) participant (elafibranor group) classified as AKI stage 3. The participant with the AKI stage 3 classification was the participant who died of acute kidney injury and biliary sepsis, which were not considered related to study drug.

Table 31: Phase 3 PBC study 319-1: occurrence of at least one serum creatinine post-baseline value >ULN (only on the subset of participants with baseline value ≤ULN) (Safety analysis set)

Period **Subset of Participants** **Category**	**Elafibranor 80 mg** **(N=108)** **n (%)**	**Placebo** **(N=53)** **n (%)**
End of 52 week treatment period		
Participants with normal baseline serum creatinine (≤ULN) (N1)	**96**	**45**
Participants with any post-baseline abnormal serum creatinine (>ULN) (N2)	**14 (14.6)**	**3 (6.7)**

Period Subset of Participants Category	Elafibranor 80 mg (N=108) n (%)	Placebo (N=53) n (%)
All participants with normal baseline and any abnormal post-baseline serum creatinine		
Did not meet AKI Stage I criteria	13 (13.5)	0
AKI Stage 1: ≥1.5 and <2.0 x baseline or change from baseline ≥ 0.3 mg/dL	1 (1.0)	0
AKI Stage 2: ≥2.0 and <3.0 x baseline	0	0
AKI Stage 3: ≥3.0 x baseline or ≥4.0 mg/dL	0	0
Last post-baseline visit		
Participants with normal baseline serum creatinine (≤ULN) (N1)	**96**	**45**
Participants with last post-baseline abnormal serum creatinine (>ULN) (N3)	**7 (7.3)**	**1 (2.2)**
All participants with normal baseline and last post-baseline abnormal serum creatinine		
Did not meet AKI Stage I criteria	5 (5.2)	0
AKI Stage 1: ≥1.5 and <2.0 x baseline or change from baseline ≥ 0.3 mg/dL	1 (1.0)	0
AKI Stage 2: ≥2.0 and <3.0 x baseline	0	0
AKI Stage 3: ≥3.0 x baseline or ≥4.0 mg/dL	1 (1.0)	0

AKI=acute kidney injury; KDIGO=Kidney Disease Improving Global Outcomes; PBC=primary biliary cholangitis; ULN=upper limit of normal

Data Source: Study 319-1

N: Number of participants in population. n: Number of participants with data available. %: Percentages are based on N1, N2 or N3 as applicable to the given subset of participants.

N1: number of participants with normal baseline serum creatinine for the 52-week treatment period. N2: number of participants with normal baseline serum creatinine for the 52-week treatment period and an abnormal serum creatinine at end of the 52week treatment period. N3: number of participants with normal baseline serum creatinine for the DB period and an abnormal serum creatinine at last post-baseline visit of the DB period.

If a participant has post-baseline results in more than one category, only the worst case is presented.

AKI stage as defined by KDIGO clinical practice guideline.

The number and percentage of participants with an increase of 25% from baseline in serum creatinine at any time during the study was 11 (10.2%) in the elafibranor group and 4 (7.5%) in the placebo group. The median baseline serum creatinine values for these participants in both treatment groups were within the normal range (44.2 to 79.6 µmol/l): 57.50 µmol/l in the elafibranor group and 57.90 µmol/l in the placebo group.

A listing of the participants who were treated with either elafibranor or placebo who had an ≥25% and ≥0.3 mg/dl increase from baseline and above the upper limit of normal are listed in **Table 32**.

Table 32: Participants with serum creatinine increase of ≥25% and ≥0.3 mg/dl from baseline

Subject ID	Treatment	Analysis Date	Study Day	Visit Name	Result (mg/dL) High/ Normal	Change from Baseline (mg/dL)	ULN (mg/dL)	Baseline Values (mg/dL) High/ Normal	Associated Adverse Event(s)
	Elafibranor 80mg	08Feb 2023	289	Unscheduled 3900.02	1.51 High	0.60	0.90	0.91 High	BUN increased; Blood creatinine increased; GFR decreased
	Elafibranor 80mg	13Dec 2022	362	Visit 6 - Week 52	1.05 High	0.35	0.90	0.70 Normal	None
		04Apr 2023	474	Last DB Visit	1.03 High	0.33	0.90	0.70 Normal	None
	Elafibranor 80mg	25Feb 2022	213	End of DB Treatment	2.91 High	2.43	0.90	0.48 Normal	Biliary Sepsis
	Placebo	01Mar 2023	581	Visit 7 - Week 78	1.70 High	0.66	0.90	1.04 High	AKI, UTI
		05Apr 2023	616	Last DB Visit	1.53 High	0.49	0.90	1.04 High	

AKI=acute kidney injury; BUN=blood urea nitrogen; DB=double-blind; GFR=glomerular filtration rate; UTI=urinary tract infection.

Urine albumin to creatinine ratio (UA/Cr)

The median baseline values were 17.0 mg/g Cr in the elafibranor group and 15.5 mg/g Cr in the placebo group, which were within the normal range (<29 mg/g Cr). At week 52, the median observed values in both treatment groups remained similar and within the normal range (18.0 mg/g Cr and 14.0 mg/g Cr, respectively).

Cystatin C

The mean (SD) cystatine C baseline values were 1.017 (0.193) mg/l in the elafibranor group and 0.986 (0.212) mg/l in the placebo group, which were within the normal range (>0.62 to 1.11 mg/l). The mean observed values in cystatin C at week 52 were 1.005 (0.168) mg/L and 1.018 (0.227) mg/L, respectively, also within normal range. The mean percentage change from baseline in cystatin C at week 52 was 0.004 (11.967%) in the elafibranor group and 3.065 (11.684%) in the placebo group. Four (4.3%) participants in the elafibranor group and 1 (2.2%) participant in the placebo group had a 25% increase from baseline in cystatin C.

Estimated glomerular filtration rate (eGFR)

Analysis of eGFR was conducted only on those participants who had a 25% increase from baseline in serum creatinine. There were no clinically meaningful findings.

Homocysteine

Homocysteine levels have not been evaluated in the clinical studies on PBC.

However, homocysteine levels were evaluated in several studies on NASH. The mean homocysteine levels remained below the upper limit of normal in both elafibranor groups (80 mg and 120 mg) after a treatment duration of 331 to 342 days (maximum 382 days) in Phase 2 study 212-7 and in the elafibranor 120 mg arm after a mean treatment duration of 102 to 103 weeks (maximum of 221 weeks) in Phase 3 study 315-1. In study 315-1, the mean and median homocysteine levels of participants with and without major adverse cardiovascular events (MACE) were comparable for both elafibranor and placebo treatment. The homocysteine levels remained within the normal range

throughout the study. No treatment-emergent adverse events of increased homocysteine levels were reported in any of the NASH studies on the clinical effects of elafibranor.

Urinalysis
In study 319-1, no clinically meaningful differences between treatment groups were noted with respect to urinalysis (dipstick) laboratory test results and changes in urinalysis from baseline by visit.

Electrocardiograms
ECG Results for the study 3191 and for the thorough QT (TQT) study in healthy participants are discussed below. The majority of the findings in other studies were normal, with few isolated abnormal results. No clinically relevant differences between treatment groups were observed.

In study 319-1, one participant (in the elafibranor group) had a post-baseline clinically significant abnormal ECG finding, which was reported as a treatment-emergent adverse event (preferred term: electrocardiogram PR prolongation). This event was mild, nonserious, and considered possibly related to the study drug.

In study 216-1, there were no clinically significant changes in the individual ECG results.

Thorough QT study in healthy participants

One TQT study was conducted (study GFT5051139). This was a double-blind, placebo controlled, single-centre, sex-stratified, parallel group study in 2 parts. Part 1 of the study was designed to determine safety and PK of elafibranor after multiple administration (14 days) of a therapeutic dose (120 mg) and a supratherapeutic dose (300 mg) in healthy male and female participants.

Part 2 was designed to evaluate (according to ICH E.14) the impact on corrected QT using Fridericia's formula (QTcF) and corrected QT using Bazett's formula (QTcB) (and secondarily on all ECG parameters) of these 2 elafibranor dose levels after multiple dose administration once daily for 14 days in healthy male and female participants; 400 mg moxifloxacin on day 14 was used as the control drug.

The TQT study analysis and results did not show any prolongation effect of elafibranor on QT interval at therapeutic and 2.5fold higher than therapeutic doses for 14 days (3.75fold higher than the 80 mg therapeutic dose for PBC). No apparent effect of elafibranor on ECG morphology was observed. Different elafibranor and GFT1007 plasma concentrations had no impact on QT interval prolongation.

Ultrasonography
In study 319-1, no participants treated with elafibranor had abnormal, clinically significant liver or bladder ultrasound results at week 52.

Bone mineral density and serum bone markers
In study 319-1, there was no significant difference in the change in bone mineral density (g/cm^2) from baseline between elafibranor and placebo.

Change from baseline in bone mineral density (hip and lumbar) T-scores assessed by DEXA scanning at week 52 are presented in **Table 33**. There was also no difference in change in T-scores from baseline between treatment groups, except for the total hip region, where an increase in T-score from baseline was noted for the elafibranor treated group compared to placebo (LS mean difference with placebo was 0.325 [95% CI: 0.056; 0.595; p=0.0186]).

Table 33: Change from baseline in bone mineral density (hip and lumbar) T-scores assessed by DEXA scanning at week 52-ANCOVA (ITT analysis set)

Parameter name	Femoral neck bone mneral density T-score		Lumbar bone mineral density T-score		Total hip bone mineral density T-score	
Analysis visit statistic	Elafibranor 80 mg	Placebo	Elafibranor 80 mg	Placebo	Elafibranor 80 mg	Placebo
	(N=108)	(N=53)	(N=108)	(N=53)	(N=108)	(N=53)
Baseline (observed)						
n	79	34	80	32	77	29
Mean (SD)	-1.359 (1.100)	-1.068 (0.997)	-1.236 (1.446)	-0.902 (0.990)	-1.136 (1.159)	-0.514 (0.994)
Median	-1.600	-1.000	-1.350	-1.000	-1.200	-0.700
Q1; Q3	-2.200; -0.700	-1.700; -0.400	-2.300; -0.150	-1.400; -0.450	-1.900; -0.300	-1.000; 0.300
Min; Max	-3.40; 1.20	-3.20; 1.30	-4.40; 2.30	-3.00; 1.60	-3.90; 1.60	-2.50; 1.20
Week 52 (Change from baseline)						
n	63	27	64	26	59	24
Mean (SD)	-0.016 (0.402)	-0.111 (0.533)	-0.006 (0.487)	-0.022 (0.405)	0.039 (0.529)	-0.371 (0.618)
Median	0	-0.100	0	0	0	-0.200
Q1; Q3	-0.200; 0.200	-0.200; 0.100	-0.200; 0.300	-0.200; 0.300	-0.200; 0.200	-0.500; 0.100
Min; Max	-2.10; 1.10	-1.70; 0.90	-1.70; 1.60	-1.40; 0.70	-2.70; 1.20	-2.00; 0.40
LSM	-0.024	-0.092	-0.023	-0.014	0.02	-0.305
95% CI	[-0.134; 0.086]	[-0.259; 0.076]	[-0.140; 0.094]	[-0.196; 0.169]	[-0.122; 0.161]	[-0.532; -0.079]
LSM difference with Placebo	0.067		-0.009		0.325	
95% CI	[-0.132; 0.267]		[-0.224; 0.206]		[0.056; 0.595]	
p-value	0.5036		0.9332		0.0186	

ANCOVA=analysis of covariance; CI=confidence interval; DEXA=dual-energy X-ray absorptiometry; ITT=intent-to-treat; LSM=least mean square; Max=maximum; Min=minimum; Q1=first quartile; Q3=third quartile; SD=standard deviation
Baseline is defined as the last non-missing central value on or before the first dose of the randomized study medication.
Analysis uses the ANCOVA model, adjusting for baseline parameter and the stratification factors.
Data Source: Study 319-1 CSR, Table 14.2.6.21

The bone mineral density T-scores at the hip level at baseline and week 52 are displayed graphically in **Figure 11**.

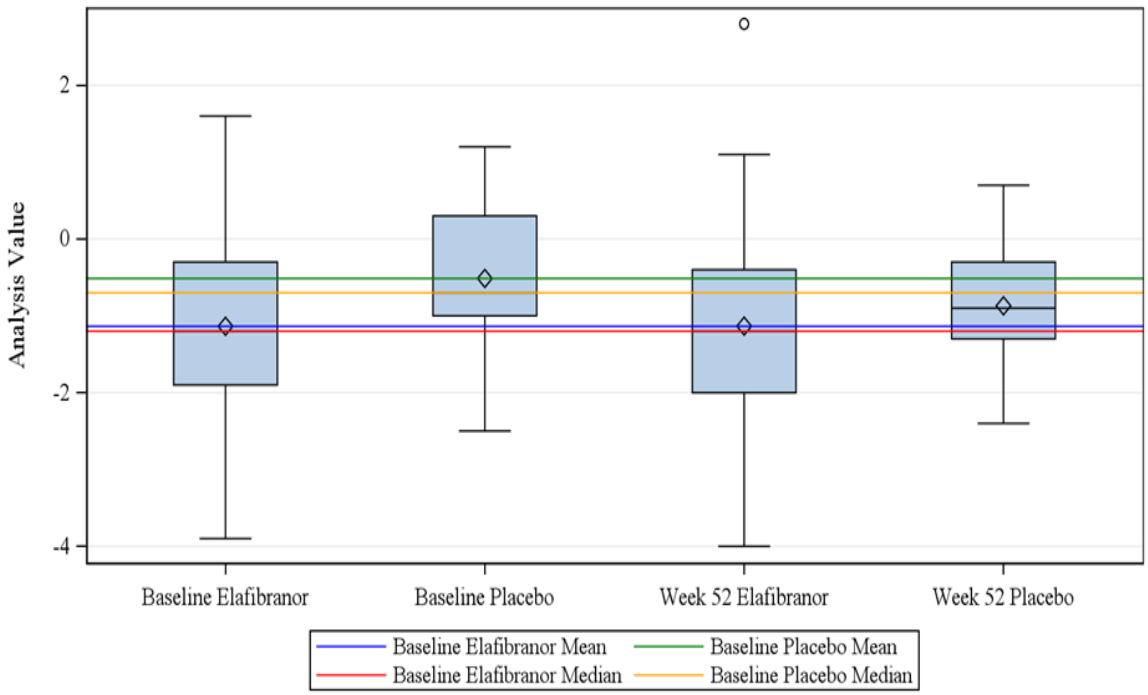


Figure 11: Bone mineral density T-scores at the hip level at baseline and week 52

Data Source: Study 319-1
Note: The box and whisker plot shows the median (diamond), interquartile range Q1 and Q3 (top and bottom of box), and the minimum and maximum (whiskers).

No significant differences were noted for increases in CTX (a marker for osteoclast activity and bone resorption) which were observed in both treatment groups or in decreases in P1NP (a marker or osteoblast activity and bone formation), which were also observed in both treatment groups.

2.6.8.5. In vitro biomarker test for patient selection for safety

No *in vitro* biomarker test for patient selection for safety was used

2.6.8.6. Safety in special populations

Participants with renal impairment

Study 118-13 was an open-label, Phase 1 study to assess the need for elafibranor dose adjustment in a renally impaired population. The study included 10 healthy male and female participants and 13 male and female participants with end stage renal disease (ESRD) not yet on dialysis. All 23 participants received a single 120 mg oral dose of elafibranor following an overnight fast (i.e. at least 10 hours).

Overall, 8 treatment-emergent adverse events were reported by 5 (21.7%) participants; 6 treatment-emergent adverse events were reported by 3 participants with ESRD and 2 treatment-emergent adverse events were reported by 2 healthy participants. Headache was reported by 2 participants (one from each group); all other treatment-emergent adverse events were reported by only 1 participant. The majority of treatment-emergent adverse events (5/8) were mild in intensity, and the 3 remaining

treatment-emergent adverse events were considered moderate in intensity. One episode of headache experienced by a healthy participant was assessed as possibly related to study treatment and resolved spontaneously after 2 days.

No deaths or serious treatment-emergent adverse events were reported. One treatment-emergent adverse events of temporo-spatial disorientation of moderate intensity and considered unrelated to study treatment led to study withdrawal in 1 participant with ESRD.

Overall, clinical laboratories (haematology, biochemistry, and urinalysis), vital signs, physical examination findings, and ECG measurements were within the appropriate reference ranges. One report of abnormal nose and throat examination in 1 ESRD participant was considered to be clinically significant; all other abnormal measurements were not considered to be clinically relevant.

According to the applicant, administration of a single dose of elafibranor 120 mg was overall well tolerated in participants with ESRD.

In the PK analysis, the total drug exposure of the parent and active metabolite was not significantly different between healthy participants and renally impaired participants. The unbound fraction of elafibranor and GFT1007 was low and relatively similar in both healthy participants and participants with ESRD. Therefore, a dose reduction of elafibranor is not necessary in patients with renal impairment.

The impact of renal function on the PK of elafibranor and GFT1007 was also evaluated in a population PK analysis. eGFR At baseline was a covariate impacting trough concentrations, but only for the metabolite GFT1007 PK model. However, forest plot analysis showed no clinically relevant effect on area under the concentration-time curve (AUC) or maximum observed drug concentration (Cmax) concentrations.

Participants with hepatic impairment

In pivotal study 319-1, one study patient in elafibranor (0.9%) and 2 in the placebo group (3.8%) had liver events adjudicated as potentially DILI.

The PK, safety, and tolerability of 120 mg elafibranor administration in males and females with mild, moderate, or severe hepatic impairment as compared with matched-control males and females with normal hepatic function was evaluated in open-label, Phase 1, single-dose, parallel-group study 118-14.

The treatment groups were as follows:

- Group 1 – normal hepatic function: N=10
- Group 2 – mild hepatic impairment (Child-Pugh Class A): N=7
- Group 3 – moderate hepatic impairment (Child-Pugh Class B): N=7
- Group 4 – severe hepatic impairment (Child-Pugh Class C): N=6

All 30 participants received the single dose of 120 mg elafibranor and all completed the study.

A total of 8 treatment-emergent adverse events were reported by 6 (20.0%) participants: 2 treatment-emergent adverse events were reported by 1 participant with severe hepatic impairment (Child-Pugh Class C), and 6 treatment-emergent adverse events were reported by 1 healthy participant. All treatment-emergent adverse events were considered mild in intensity. No treatment-emergent adverse event was reported more than once. Of the 8 treatment-emergent adverse events reported, 4 treatment-emergent adverse events (including 2 reported by the participant with severe

hepatic impairment) were considered not related and the remaining 4 treatment-emergent adverse events reported by the healthy participant were considered unlikely related.

There were no deaths, serious treatment-emergent adverse events, or other significant adverse events reported in this study.

Overall, clinical laboratories (haematology [including coagulation], biochemistry, and urinalysis) were within the normal reference ranges. One report of white blood cells present in urine in one healthy participant was clinically significant; all other abnormal measurements, including those reported for alanine aminotransferase, alkaline phosphatase, albumin, and total bilirubin were not considered to be clinically relevant.

Mean values for vital signs and ECG parameters were within normal ranges at all timepoints. Abnormalities in vital signs, physical examination, and ECG were observed for a number of parameters at one or more assessments. The abnormal values generally occurred in participants with low or high baseline values that were not notably different from the post-dose results and were not considered to be clinically relevant.

It was concluded that the administration of elafibranor was well tolerated in healthy and hepatically impaired participants following a single oral dose of 120 mg under fasting conditions.

The PK analysis showed that the total drug exposure of the parent drug and active metabolite was not significantly different between healthy participants and participants with hepatic impairment. This was consistent with population PK analysis which concluded that PK profile based on total circulating levels of elafibranor and GFT1007 were not different in hepatically impaired participants, compared with those with normal hepatic function. However, the unbound fraction of elafibranor increased by approximately 2fold, and the unbound fraction of the metabolite GFT1007 increased by approximately 2.7fold in the severe hepatic impairment cohort.

Elafibranor has not been studied in participants with PBC with severe hepatic impairment. Use in patients with severe hepatic impairment (Child-Pugh C) is therefore not recommended.

Study in young versus elderly participants

Study 319-1

In the pivotal study 319-1, 21.7% of study patients were ≥65 years. In an additional analysis, the observed treatment-emergent adverse events were categorized in the following age categories: <65 years, 65 to 74 years and 75 to 84 years, and ≥85 years (**Table 34**).

Table 34: Treatment emergent adverse events by age category

Adverse event category/ preferred term	Elafibranor				Placebo			
	Age category (years)				Age category (years)			
	<65	65-74	75-84	≥85	<65	65-74	75-84	≥85
	(N = 83)	(N = 24)	(N = 1)	(N = 0)	(N = 43)	(N = 7)	(N = 3)	(N = 0)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total adverse events	80 (96.4%)	23 (95.8%)	1 (100.0%)	0	39 (90.7%)	6 (85.7%)	3 (100.0%)	0
Serious adverse events – Total	6 (7.2%)	5 (20.8%)	0	0	6 (14.0%)	1 (14.3%)	0	0
- Fatal	0	2 (8.3%)	0	0	0	0	0	0

Adverse event category/ preferred term	Elafibranor				Placebo			
	Age category (years)				Age category (years)			
	<65	65-74	75-84	≥85	<65	65-74	75-84	≥85
	(N = 83)	(N = 24)	(N = 1)	(N = 0)	(N = 43)	(N = 7)	(N = 3)	(N = 0)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Hospitalization/prolong existing hospitalization	5 (6.0%)	4 (16.7%)	0	0	5 (11.6%)	1 (14.3%)	0	0
- Life-threatening	0	0	0	0	0	0	0	0
- Disability/incapacity	0	2 (8.3%)	0	0	0	0	0	0
- Other (medically significant)	2 (2.4%)	0	0	0	2 (4.7%)	0	0	0
Adverse event leading to drug discontinuation	5 (6.0%)	6 (25.0%)	0	0	5 (11.6%)	0	0	0
Adverse event leading to discontinuation from study	2 (2.4%)	3 (12.5%)	0	0	2 (4.7%)	0	0	0
Psychiatric disorders	6 (7.2%)	1 (4.2%)	0	0	5 (11.6%)	1 (14.3%)	0	0
Nervous system disorders	18 (21.7%)	6 (25.0%)	0	0	12 (27.9%)	2 (28.6%)	1 (33.3%)	0
Accidents and injuries	13 (15.7%)	4 (16.7%)	1 (100.0%)	0	7 (16.3%)	0	1 (33.3%)	0
Cardiac disorders	2 (2.4%)	3 (12.5%)	0	0	2 (4.7%)	0	1 (33.3%)	0
Vascular disorders	6 (7.2%)	2 (8.3%)	0	0	2 (4.7%)	1 (14.3%)	0	0
Cerebrovascular disorders	0	1 (4.2%)	0	0	0	0	0	0
Infections and infestations	52 (62.7%)	15 (62.5%)	1 (100.0%)	0	24 (55.8%)	4 (57.1%)	3 (100.0%)	0
Anticholinergic syndrome	12 (14.5%)	1 (4.2%)	0	0	0	2 (28.6%)	2 (66.7%)	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	11 (13.3%)	3 (12.5%)	1 (100.0%)	0	4 (9.3%)	0	2 (66.7%)	0
Loss of consciousness	0	0	0	0	0	0	0	0
Syncope	0	0	0	0	1 (2.3%)	0	0	0
Dizziness	4 (4.8%)	0	0	0	0	0	1 (33.3%)	0

Adverse event category/ preferred term	Elafibranor				Placebo			
	Age category (years)				Age category (years)			
	<65	65-74	75-84	≥85	<65	65-74	75-84	≥85
	(N = 83)	(N = 24)	(N = 1)	(N = 0)	(N = 43)	(N = 7)	(N = 3)	(N = 0)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ataxia	0	0	0	0	0	0	0	0
Fall	3 (3.6%)	1 (4.2%)	1 (100.0%)	0	1 (2.3%)	0	1 (33.3%)	0
Fracture	5 (6.0%)	3 (12.5%)	0	0	0	0	0	0
Adverse events more frequently in older patients	34 (41.0%)	14 (58.3%)	0	0	23 (53.5%)	1 (14.3%)	3 (100.0%)	0
Covid-19	21 (25.3%)	10 (41.7%)	0	0	16 (37.2%)	1 (14.3%)	3 (100.0%)	0
Pruritus	16 (19.3%)	6 (25.0%)	0	0	13 (30.2%)	1 (14.3%)	0	0

Overall, the proportion of participants reporting any treatment-emergent adverse event was similar across the age groups. The frequency of treatment-emergent adverse events in participants <65 years treated with elafibranor was 96.4% (N=83) compared to 90.7% (N=43) for the age matched placebo participants. The frequency of treatment-emergent adverse events in participants 65 to 74 years treated with elafibranor was 95.8% (N=24) compared to 85.7% (N=7) for the age matched placebo participants.

The adverse drug reactions and their corresponding incidences in participants treated with elafibranor in study 319-1 by age category (<65 years and ≥65 years) are presented in Table 35. Overall, 40/83 (48%) of participants in the <65 years age group compared to 7/25 (28%) participants in the ≥65 years age group experienced an adverse drug reaction.

Table 35: Adverse drug reactions and corresponding incidences by age category in participants with PBC treated with elafibranor 80 mg in study 319-1

Adverse drug reaction, n (%)	Elafibranor 80 mg	
	<65 years	≥65 years
	(N=83)	(N=25)
Abdominal pain [a]	11 (13.3)	1 (4)
Diarrhoea	12 (14.5)	0
Nausea	11 (13.3)	1 (4)
Vomiting	11 (13.3)	1 (4)
Constipation	8 (9.6)	1 (4)
Headache	8 (9.6)	1 (4)
Cholelithiasis	2 (2.4)	1 (4)
Myalgia	3 (3.6)	0
Blood creatine phosphokinase increased	3 (3.6)	1 (4)
Blood creatinine increased	0	1 (4)

[a] Includes PTs of Abdominal pain, Abdominal pain upper and Abdominal pain lower.

Study 119-16

The clinical effects of elafibranor in younger and older healthy volunteers have been evaluated in study 119-16. Study 119-16 was a Phase 1 study to evaluate the PK, safety, and tolerability of a single dose of 120 mg elafibranor in 11 healthy elderly male and female participants (≥75 years old; mean age

76.7 years) compared to 10 healthy young male and female participants (18–45 years old; mean age 34.7 years [actual range: 26 to 42 years]). All 21 participants completed the study.

Overall, 16 treatment-emergent adverse events were reported in 8 (38.1%) participants; 8 treatment-emergent adverse events were reported in 3 young participants and 8 treatment-emergent adverse events were reported in 5 elderly participants. The only treatment-emergent adverse event reported in more than 2 participants was headache, reported in 5 (23.8%) participants overall (2 young participants and 3 elderly participants). All treatment-emergent adverse events were reported as mild in intensity except for 2 treatment-emergent adverse events reported as moderate in intensity (one treatment-emergent adverse events of back pain in one young participant and one treatment-emergent adverse events of nasopharyngitis in one elderly participant). A total of 3 treatment-emergent adverse events in 2 (18.2%) elderly participants were considered possibly related to treatment: 2 events of mild diarrhoea and 1 event of mild headache. The remaining treatment-emergent adverse events were considered unlikely related to treatment (4 treatment-emergent adverse events in 2 participants) or not related to treatment (9 treatment-emergent adverse events in 5 participants).

There were no deaths, serious treatment-emergent adverse events, or other significant adverse events reported in this study.

Overall, clinical laboratories (haematology, biochemistry, and urinalysis) were within the normal reference ranges, showed little change throughout the study, and did not show any relevant differences between the two participant groups. Aside from 1 report of low neutrophils reported in 1 young participant that was considered clinically relevant according to the investigator, all other abnormal laboratory values were not considered clinically relevant, including two potentially clinically significant abnormal values (high eosinophils and high potassium observed in one elderly participant each).

Mean values for vital signs and ECG parameters remained within the normal reference range and showed little change throughout the study. Differences in parameters and examinations between the two groups were expected due to differences in age and lifestyle. Aside from abnormal findings of the gastrointestinal system in 1 young participant on day 10 of the study (which was considered clinically relevant and associated with a treatment-emergent adverse event of mild abdominal pain), no other abnormal findings were considered clinically relevant by the investigator.

According to the applicant, the safety results showed that a single oral administration of elafibranor 120 mg to young and elderly participants was well tolerated, with no differences between the two populations.

Based on the limited number of healthy participants in this study (10 young adults and 11 elderly), the plasma exposure and peak plasma concentration of the active metabolite GFT1007 appeared to increase by approximately 50% in healthy elderly participants. However, population PK analyses concluded that in participants treated with elafibranor, age did not have a clinically significant impact. These conclusions are also in line with the safety data from study 319-1 where the impact of age was assessed. Therefore, no elafibranor dose adjustment is required based on age according to the applicant.

Use in pregnancy and lactation

Pregnancy

There were no pregnancy or pregnancy related events reported in the PBC studies.

Overall, 17 pregnancies (4 following maternal exposure and 13 following paternal exposure [in female partners of male participants]) have been reported in the ongoing and completed clinical studies for

different indications since 1 August 2006 to the date 31 July 2023. Outcomes for all maternal exposures (4) and most paternal exposures (8) were available at time of submission of this application; outcomes for the other paternal exposure (5) remain outstanding.

Besides the cases discussed below of 2 serious events of spontaneous abortion and 1 serious event of neonatal respiratory distress syndrome following premature delivery, none of the pregnancies met any seriousness criteria and none were associated with adverse events at time of reporting.

Maternal exposures

Pregnancy was reported in 4 female participants following exposure to elafibranor.

In 2 female participants, the pregnancy evolved normally and resulted in birth of healthy babies at term (gestational age ≥37 weeks).

> One participant (in study 2127) became pregnant 6 months after the last elafibranor 80 mg dose.
>
> The other participant (in study 3151) had her last menses after almost 9 months of study drug exposure (elafibranor 120 mg once daily). One month later, the study drug was withdrawn following positive pregnancy test.

In the other 2 female participants, the pregnancy resulted in a serious treatment-emergent adverse event of spontaneous abortion.

> In the first case, the spontaneous abortion at approximately 4 weeks of gestation occurred after 5 months (study day 158) of treatment with elafibranor 80 mg in a 20- 25year-old female participant (first pregnancy) with NASH (in study 212-7); the study treatment had been withdrawn on study day 152 when the participant was found to be pregnant. She had a relevant medical history.
>
> In the second case, the spontaneous abortion occurred after 13 months (study day 434) of treatment with elafibranor 120 mg (gestational age 7 weeks 4 days) in an obese participant with NASH (in study 3151). The study treatment had been withdrawn on study day 408 when the participant was found to be pregnant).

Causal relationship to study drug was considered a reasonable possibility by both investigator and sponsor for both events.

Paternal exposures

Pregnancy was reported in 13 female partners of males receiving elafibranor treatment.

In 7 pregnant females (following paternal exposure), the pregnancy evolved normally and resulted in birth of healthy babies at term (gestational age ≥37 weeks).

One pregnancy following paternal exposure (in study 3151) resulted in premature delivery (gestational age 33 weeks) in a mother who experienced serious events of gestational hypertension and pre-eclampsia (not related to the paternal study drug exposure). The neonate presented with moderate respiratory distress syndrome which resolved completely at 8 weeks following delivery.

For the remaining 5 cases, all following paternal exposure, no additional data could be obtained as the female partners of the participants did not wish to sign informed consent for follow-up on pregnancy.

Lactation

There were no lactation or lactation related events (including exposure to infants via milk transfer) reported in the ongoing and completed clinical studies since 01 August 2006 to the date 31 July 2023.

Published effects of PPAR agonists on pregnancy, lactation, and fertility

A systematic review of all available (clinical and nonclinical) published literature covering a period from 1980 to May 2023 was performed regarding the use of PPAR agonists in pregnant and lactating women and the effects of the drug on male and female fertility. A total of 4 publications were identified and considered relevant. Excluded publications include those that reported on natural and synthetic (e.g., rosiglitazone) PPARγ agonists; these were not considered relevant based on the known affinity of elafibranor for PPARα.

Overall, treatment of pregnant female rodents with PPARα agonists, including but not limited to perfluorinated alkyl acids, clofibrate, and Wy-14,643, results in notable effects on the ability to maintain a healthy pregnancy and foetal development (Nyitray 1980; Abbott 2009; Palkar 2010; Nishimura 2013). Exposure to PPARα during gestation resulted in decreases in the overall number of foetuses per litter, the number of live foetuses per litter, number of implantations, and foetal body weights and resulted in increases in neonatal death and percent litter lost (Nyitray 1980; Abbott 2009; Palkar 2010; Nishimura 2013). Growth defects and foetal developmental delays were inconsistently reported (Abbott 2009; Nishimura 2013). Foetal liver weight was increased in newborn rats following maternal treatment with PPARα agonists, but these effects were reversible following 1 week without treatment (Nyitray 1980). In Nishimura, both placental malformation and presence of placental cysts were reported. The extent of the effects discussed were dependent on the amount of PPARα administered to pregnant females and timing of administration during gestation (Nyitray 1980; Abbott 2009; Palkar 2010; Nishimura 2013).

Studies in other indications

Except for safety risks that were reported with respect to elafibranor exposure and pregnancy, the observed safety risks of elafibranor in other conditions (see exposure section above) are overall comparable with those of elafibranor in PBC patients.

2.6.8.7. Immunological events

No data on particular immunological events were submitted.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Several drug interaction studies were conducted, which are discussed and assessed in the pharmacology part of this assessment report.

Co-administration with elafibranor was well tolerated by the study participants. No treatment-related treatment-emergent adverse events were observed in the conducted interaction studies.

2.6.8.9. Discontinuation due to adverse events

Phase 3 PBC study 319-1

Eleven (10.2%) participants in the elafibranor group and 5 (9.4%) participants in the placebo group experienced treatment-emergent adverse events that led to treatment discontinuation. The only treatment discontinuation event occurring in >1 participant in the elafibranor group was blood creatine phosphokinase (CPK) increased (4 participants, 3.7%).

Phase 2 PBC study 216-1

In study 216-1, there were no other treatment-emergent adverse events that led to study treatment discontinuation except for one participant in the elafibranor 120 mg group who experienced serious treatment-emergent adverse events of ischemic stroke and post procedural stroke (both unrelated to study treatment) within 24 hours of first study treatment intake.

2.6.9. Discussion on clinical safety

Data collection. The elafibranor clinical development program currently comprises a total of 31 clinical studies. The clinical safety of elafibranor in PBC patients has been evaluated in Phase 2 study 216-1, and the pivotal Phase 3 study 319-1. Study results of the double-blind treatment period of both studies have been submitted (study 216-1: 12 weeks, study 319-1: 52 weeks). The clinical safety of elafibranor 80 mg once daily in PBC patients is further evaluated in the ongoing long-term extension period of study 319-1.

The applicant described appropriately when particular safety evaluations were conducted in studies 216-1 and 319-1. A clinical experts committee adjudicated particular safety endpoints, including liver transplantation and death. The evaluated safety endpoints are considered relevant.

Patient exposure. Non-pooled safety data from individual clinical studies were presented, due to differences in the study populations, study durations, and elafibranor dosages. In total, 206 PBC patients have been included in study 319-1 (n= 161) and study 216-1 (n= 45). Of these, 138 PBC patients were exposed to elafibranor (study 319-1: 108, study 216-1: 30). Mean exposure to elafibranor 80 mg once daily (n= 108) was 66.2 weeks (range 1.1–104.1 weeks) in study 319-1. In study 216-1, mean exposure to elafibranor 80 mg once daily (n= 15) was 85.7 days (range 80-106 days) and mean exposure to elafibranor 120 mg once daily (n= 15) was 85.1 days (range 83-87 days).

Studies on elafibranor have also been conducted in patients with other conditions, namely non-alcoholic steatohepatitis (NASH; n= 2,434), non-alcoholic fatty liver disease (NAFLD; n= 17), diabetes mellitus (n= 109), overweight and/or abnormal glucose tolerance (n= 129), dyslipidaemia/hyperlipidaemia (n= 131). Studies on elafibranor have also been conducted in several special populations, namely patients with renal impairment (n= 13), hepatic impairment (n= 20), and healthy participants (n=686). In total, 3,745 subjects have been evaluated, of whom 2,588 have been exposed to elafibranor. 2,463 Participants were exposed to elafibranor dosages of 80 up to 360 mg/day. 1,723 Of the 2,588 (66.6%) Participants were exposed to elafibranor for ≥52 weeks in the completed clinical studies.

The number of PBC patients who were exposed to elafibranor is limited (n= 206). Since elafibranor is a first in class drug, it is not possible to rely on the safety profile of elafibranor in other authorised indications. However, considering that PBC is a rare disease with prevalence estimates ranging from 1.9 to 40.2 cases per 100,000 persons[1], and also that the total exposure to elafibranor is in line with ICH E1 guidance (1994), the total elafibranor exposure to PBC and other conditions is acceptable to support current marketing authorisation application of elafibranor for PBC.

Adverse events

In study 319-1, **treatment-emergent adverse events** tended to be reported more frequently among study patients who were exposed to elafibranor 80 mg as compared to placebo once daily (respectively

[1] Floreani et al. Prevalence of familial disease in primary biliary cirrhosis in Italy. Journal of Hepatology. Volume 26, Issue 3, March 1997, pages 737-738.

96.3 versus 90.6%). In both treatment groups, the maximum severity of treatment-emergent adverse events was mild to moderate (elafibranor 80 mg: 89.8%, placebo: 88.7%).

In study 216-1, the proportions of study patients who experienced treatment-emergent adverse events during treatment with elafibranor 80 and 120 mg, and placebo once daily were respectively 80%, 86.7% and 80%. In line with study 319-1, the severity of treatment-emergent adverse events was mild to moderate in the patients who were treated with elafibranor 80 and 120 mg, or placebo treatment once daily (86.7% in each of these groups).

Most frequently reported treatment-emergent adverse events

In study 319-1, treatment-emergent adverse events reported in ≥5% of participants in the elafibranor group and with a higher incidence than the placebo group (difference >1%) were mostly gastrointestinal in nature and transient, including vomiting (11.1 versus 1.9%), diarrhoea (11.1 versus 9.4%), nausea (11.1 versus 5.7%), constipation (8.3 versus 1.9%), abdominal pain upper (7.4 versus 5.7%), and gastro-oesophageal reflux disease (6.5 versus 1.9%). The other events were arthralgia (8.3 versus 3.8%) and upper respiratory tract infection (6.5 versus 3.8%).

The following treatment-emergent adverse events in study 319-1 tended to occur less frequently in elafibranor-treated as compared to placebo-treated study patients: pruritus (20.4 versus 26.4%), fatigue (9.3 versus 13.2%), COVID-19 (28.7 versus 37.7%), urinary tract infection (11.1 versus 18.9%), and headache (8.3 versus 11.3%).

In study 216-1, the most frequently reported treatment-emergent adverse events occurring in 2 or more study patients on elafibranor 80 mg and at a higher frequency than placebo were viral upper respiratory tract infection, dizziness, headache, and pruritus.

Overall, the nature of the most frequently reported treatment-emergent adverse events is treatable and transient.

Updated safety data (additional 4 months) on elafibranor from the long-term extension period of study 319-1, suggested a safety profile comparable to that previously reported. No new safety concerns were identified. However, the safety profile of elafibranor beyond this additional evaluation period is yet unknown. Long-term safety data may provide additional insight into its tolerability and safety profile including hepatic and renal function and its target selectivity. Long term safety will be followed up as missing information with additional pharmacovigilance activities as described in the RMP and in the planned imposed post-authorisation study (ELFINITY)

Adverse drug reactions

In study 319-1, treatment-related treatment-emergent adverse events were observed at a comparable frequency in study patients who were exposed to elafibranor 80 mg (38.9%) and placebo once daily (39.6%).

The most commonly reported adverse drug reactions associated with elafibranor treatment which occurred in more than 10% of participants and with a higher incidence than in the placebo group (n = 53; difference >1%) were abdominal pain (11.1% versus 5.7%), diarrhoea (11.1% versus 9.4%), nausea (11.1% versus 5.7%), and vomiting (11.1% versus 1.9%). These were non-serious, mild to moderate, occurred early in treatment and tended to resolve within days to a few weeks without any dose modification or supportive measures. The most common adverse drug reaction leading to treatment discontinuation was blood CPK increased (3.7%). They have been included in the SmPC to mitigate the occurrence of the particular adverse drug reactions.

Adverse events of special interest

In study 319-1, predefined adverse events of special interest (including hepatic, renal, and muscle injury) tended to be observed more frequently in study patients who were treated with elafibranor 80 mg (29.6%) than those who were treated with placebo once daily (26.4%). This tendency also applies to the occurrence of treatment-related adverse events of special interest (6.5 vs. 3.8%), serious adverse events of special interest (4.6 vs. 1.9%), and adverse events of special interest leading to death (0.9 vs. 0%) or treatment discontinuation (5.6 vs. 1.9%).

Adverse events of special interest have not been defined and evaluated in study 216-1.

Adverse events of special interest with respect to the liver, CPK elevations and muscle injury, renal injury, the central nervous system, and major adverse cardiovascular events are discussed below.

Liver

Three study participants met the pre-specified laboratory criteria for drug-induced liver injury (DILI), one in the elafibranor group (0.9%) and two in the placebo group (3.8%). According to the clinical events committee, DILI was possible in the elafibranor-treated study patient, and probably in the two placebo-treated study patients. Based on the case description of the elafibranor-treated study patient, it is agreed that DILI is possible in this study participant. However, DILI may also be due to other causes (e.g. concomitant pharmacological treatment).

For the transaminases (AST and ALT), no evident difference was observed between elafibranor and placebo. For ALP, as expected from efficacy data, the number of subjects with ALP above the normal range was markedly lower in elafibranor than placebo. In general, liver disorders were more frequent in elafibranor (7.4 vs 1.9%) and in particular cholelithiasis (n=3 vs 0). This information has been reflected at the 4.8 section of the SmPC. In addition, a warning with respect to liver-related adverse events has been included in the SmPC. Hepatic events are also listed as an important potential risk in the RMP.

CPK elevations, muscle injury

Four (3.7%) participants in the elafibranor group (and none in the placebo group) had CPK elevations leading to drug discontinuation. All events were non-serious, and 1 was moderate in intensity. Three of the 4 cases were assessed as possibly related to study drug. No clear trend was observed in time to onset of these events (range: 29-288 days). In 2 of the 4 cases, the CPK was >5 x ULN. One case was associated to renal injury (probably as consequence of muscle injury). In all cases, the participants had concomitant disease (autoimmune thyroiditis, chronic kidney disease) or concomitant medications (statins) known to be associated with CPK elevations. A prescription to monitor CPK in some circumstances is proposed in the SmPC. This is agreed. Myopathy including rhabdomyolysis is listed as an important potential risk in the RMP.

Renal injury

Three (2.8%) participants in the elafibranor group and 1 (1.9%) participant in the placebo group had an adverse event of special interest of renal injury (all of these events were serious). An elafibranor participant with moderate event of acute kidney injury had rhabdomyolysis. In the second participant in the active treatment, the acute kidney injury was concurrent with biliary sepsis and multi-system involvement and was considered contributory to the fatal outcome. In the third participant, the acute renal failure occurred in the setting of postoperative multiorgan failure which also had a fatal outcome (and was considered unrelated to the study drug). Two of the events occurred in the setting of a complex clinical condition of systemic involvement and deterioration leading to death, and in both of those cases, the acute kidney injury was considered unrelated to the study drug. The other acute

kidney injury event occurred in the context of rhabdomyolysis and assessed as possibly related to the study drug. It is agreed with the applicant that the only event for which a clear causal association could be hypothesised is the one due to rhabdomyolysis (for creatinine increase; see below).

Central nervous system

One (0.9%) participant in the elafibranor group experienced a serious treatment-emergent adverse event of moderate tremor that led to study drug discontinuation. This participant also experienced a serious treatment-emergent adverse event of parkinsonism with uncertain adjudication. Therefore, from the clinical data available, it is not clear whether the tremor could be related to elafibranor and it is, thus, agreed that it should be considered as possibly related (and followed with routine pharmacovigilance activities). Overall, however, nervous system disorders were slightly less frequent in elafibranor than placebo (22.2% vs 28.3%).

Major adverse cardiovascular events (MACE)

In study 319-1, two (1.9%) participants in the elafibranor group experienced MACE. One participant had a serious treatment-emergent adverse event of haemorrhagic stroke. The other participant had a serious treatment-emergent adverse event of heart failure with preserved ejection fraction, which was severe. The treatment-emergent adverse events in both participants were considered unrelated to elafibranor treatment. Both participants died (of multi-system organ failure and of acute kidney injury and biliary sepsis, respectively). MACE have not been observed in the placebo arm of study 319-1.

In the Phase 3 study 315-1 on NASH with 2,150 participants followed up for a mean duration of approximately 2 years (102 weeks), a slightly higher proportion of participants in the elafibranor 120 mg group (2.0%) compared to placebo (0.7%) had MACE. Despite no differences observed in the baseline disease characteristics between the treatment groups, a slight difference was noted in medical histories between the elafibranor and placebo groups including hypertension, hyperlipidaemia, angina pectoris, coronary artery disease myocardial infarction, atrial septal defect acute myocardial infarction In study 315-1 and other clinical studies on NASH, there were no clinically meaningful changes for homocysteine, and other cardiac safety markers (NT-pro BNP and troponin T) that were evaluated and no differences were observed between the elafibranor and placebo groups.

Serious treatment-emergent adverse events

In study 319-1, serious treatment-emergent adverse events tended to be reported less frequently in study patients who were treated with elafibranor 80 mg (10.2%) than those who were treated with placebo once daily (13.2%). Serious treatment-emergent adverse events reported for >1 participant in the elafibranor group were acute kidney injury (2.8%) and hip fracture (1.9%). No other serious treatment-emergent adverse events were reported for >1 participant in either of the treatment groups, and no trend was observed.

However, serious treatment-emergent adverse events that were related to study medication tended to be observed more frequently in study patients who were treated with elafibranor 80 mg (2.8%) than those who were treated with placebo once daily (1.9%).

In study 216-1, serious treatment-emergent adverse events were observed in two study participants who were treated with elafibranor 120 mg once daily (13.3%), but not in study participants who were treated with elafibranor 80 mg or placebo once daily. This also applies to serious treatment-emergent adverse events that were related to study medication (6.7%). The reported serious treatment-emergent adverse events were autoimmune hepatitis (possibly related), and ischemic stroke (not related) and post procedural stroke (not related).

Treatment-emergent adverse events leading to treatment discontinuation

In study 319-1, the proportions of study participants who experienced treatment-emergent adverse events leading to treatment discontinuation upon treatment with elafibranor 80 mg and placebo once daily were comparable (respectively 10.2 and 9.4%). This also applies to the proportions of study participants who experienced treatment-related treatment-emergent adverse events leading to treatment discontinuation (respectively 8.3% and 7.5%). The only treatment discontinuation event occurring in >1 participant in the elafibranor group was blood creatine phosphokinase (CPK) increased (3.7%).

In study 216-1, one study patient (6.7%) who was treated with elafibranor 120 mg once daily experienced treatment-emergent adverse events that led to study treatment discontinuation.

Serious treatment-emergent adverse events leading to treatment discontinuation

In study 319-1, the proportions of study participants who experienced serious treatment-emergent adverse events leading to treatment discontinuation was comparable for study participants who were treated with elafibranor 80 mg (2.8%) or placebo once daily (1.9%). The same applies to the treatment-related treatment-emergent adverse events that led to treatment discontinuation (1.9% in both treatment groups).

Serious treatment-emergent adverse events leading to death

In study 319-1, the proportions of study participants (two 60-65-year female study patients) who experienced serious treatment-emergent adverse events leading to death tended to be higher in study participants who were treated with elafibranor 80 mg (n=2; 1.9%) as compared to placebo once daily (0%). The fatal serious treatment-emergent adverse events were multiple organ dysfunction syndrome in one participant, and biliary sepsis and acute kidney injury in the other participant. One study participant died after 30 days from elective surgery for abdominal hernia, and the cause of death was considered related to post-surgical complications. The other study participant had relevant medical history. The death occurred following biliary sepsis and acute kidney injury, assessed as not related to the study drug. From the narratives provided, it is agreed that the two participants seemed to suffer from concomitant health problems that could have led to death, and no clear evidence for a strong causative role of the elafibranor can be inferred.

Deaths were not observed in study 216-1.

Safety in special populations

Renal and hepatic impairment

The effects of elafibranor have been evaluated in patients with renal impairment (study 118-13: single elafibranor 120 mg oral dose in 23 participants with renal impairment), and hepatic impairment (study 118-14: single elafibranor 120 mg oral dose in 30 participants with varying degrees of hepatic impairment (up to Child-Pugh class C)). A single dose of elafibranor 120 mg was well-tolerated in these participants. Hence, the currently available indicate that no adjustment of the elafibranor dosing is needed in patients with renal or hepatic impairment.

Age

In the pivotal study 319-1, 21.7% of study participants were ≥65 years. In this age category (in the elafibranor arm) a higher percentage of participants with serious treatment-emergent adverse events was higher than in the category 18-64 years group (22.7% vs 7.0%). An opposite trend was observed in the placebo arm.

The effects of a single elafibranor 120 mg dose have been evaluated and compared between 21 healthy volunteers of different age (18-45 years (n= 10), ≥75 years (n= 11); study 119-16). The administered elafibranor dose was well tolerated in both age groups, with no differences between the populations. Hence, no elafibranor dose adjustment based on age is necessary.

Body mass index

In study 319-1, the observed safety risks of study patients with different BMI (≥18.5 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2) were similar within and between treatment groups. Because of this, it is concluded that BMI has no relevant impact on the safety profile of elafibranor in PBC patients with a BMI ≥18.5 kg/m^2.

Pregnancy

No pregnancy or pregnancy related adverse events were reported in studies in which the clinical effects of elafibranor were evaluated in PBC patients. However, 17 pregnancies were reported in studies in which the effects of elafibranor were evaluated for other conditions from 1 August 2006 up to 31 July 2023. The outcomes of the pregnancies that were observed after maternal exposure (n= 4: 2 normal gestation, 2 spontaneous abortion), and paternal exposure (n= 13: 7 normal gestation, 1 premature delivery (week 33), 5 unknown) varied. No lactation or lactation-related events were observed during the observation period.

From pre-clinical studies it is known that treatment of pregnant female rodents with peroxisome proliferator-activated receptor alpha (PPAR-alpha) agonists results in notable effects on the ability to maintain a healthy pregnancy and foetal development (Nyitray 1980; Abbott 2009; Palkar 2010; Nishimura 2013).

Although no safety risks of elafibranor with respect to pregnancy and lactation in PBC patients have been reported thus far caution is needed considering the limited data in PBC patients, the observed safety risks of elafibranor with respect to human pregnancies in other indications and observations in non-clinical studies. Foetotoxicity and/or teratogenicity is listed as an important potential risk in the RMP. The use of elafibranor is contra-indicated in women with a known or suspected pregnancy and in women of childbearing age who do not use contraception. Furthermore, the SmPC advises on effective contraception during and for 3 weeks after elafibranor treatment and to check the pregnancy status of patients of childbearing potential prior to initiation of elafibranor treatment. Moreover, the elafibranor should not be used during breastfeeding and for at least 3 weeks following the last dose of elafibranor as it is unknown whether elafibranor or its metabolites are excreted in human milk and a risk to the suckling child cannot be excluded. These risk mitigating measures are acceptable.

Other indications

Except for safety risks that were reported with respect to elafibranor exposure and pregnancy, the observed safety risks of elafibranor in other conditions (see exposure section above) are overall comparable with those of elafibranor in PBC patients.

Due to limited available data, the safety profile of elafibranor in male, non-white PBC patients of different ethnicity is unknown. The applicant explained later based on the available safety data on a higher elafibranor dosage (120 mg once daily) that the safety profile of this elafibranor dosage is comparable in male and female, and white and non-white NASH patients.

Drug-drug interactions and other interactions

Drug interaction studies were conducted with elafibranor and the following co administered drugs: simvastatin (study 109 5), sitagliptin (study 109 6), warfarin (study 112 8), atorvastatin (study 115

11), and indomethacin (study 119 15). All studies concluded that co-administration with elafibranor was well tolerated by the study participants. A warning with respect to CPK elevations in general and CPK elevations in combination with muscle injury during concomitant use of HMG CoA reductase inhibitors (e.g. statins) is included in the product information.

Laboratory and other findings

Haematology parameters

No clinically relevant differences between treatment groups were noted for any haematologic values over time. However, the proportion of patients with elevated international normalised ratio (INR) ≥1.5 x ULN tended to be higher in elafibranor-treated as compared to placebo-treated participants (respectively 1.9% and 0%). It was explained that the observed INR elevations (2 participants) was a chance finding in one participant, and due to apixaban treatment for paroxysmal atrial fibrillation in another participant. In both cases the observed INR elevations were considered unrelated to elafibranor treatment.

Chemistry parameters

With some exceptions, chemistry parameters including total bilirubin levels, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, cystatine C levels, and urinalysis were overall comparable for the elafibranor 80 mg and placebo once daily treatment groups in study 319-1.

One exception is that the observed decreases in elevated alkaline phosphatase levels at baseline tended to be larger for elafibranor 80 mg (-117.7 U/l) as compared to placebo once daily (-8.8 U/l) at week 52 (see clinical efficacy).

Another exception is that the proportions of patients who had normal serum creatinine levels at baseline but abnormal serum creatinine levels after baseline tended to be higher in participants who were treated with elafibranor 80 mg once daily (14.6%) as compared to those who were treated with placebo once daily (6.7%). Also, the proportion of participants with an increase of 25% from baseline in serum creatinine at any time during the study tended to be higher during elafibranor as compared to placebo treatment (10.2 vs. 7.5%). In one elafibranor-treated participant, increases in serum creatinine (0.33-0.35 mg/dl) extended slightly above the threshold of 0.3 mg/dl for acute kidney injury stage 1 (according to criteria of the Kidney Disease Improving Global Outcomes, KDIGO). According to the applicant this increase was rather due to an increase in metabolic production of creatinine due to PPAR agonism than to renal dysfunction. However, direct effects of elafibranor on renal function cannot be excluded at present. Creatine increase is an adverse drug reaction in the SmPC.

As far as evaluated, the observations with respect to laboratory evaluations in Phase 2 study 216-1 are overall in line with those in study 319-1.

In non-clinical studies, increased homocysteine levels were observed after repeated doses in both rats and monkeys (see non-clinical assessment). This effect is low to moderate in terms of severity, not dose-related and/or not consistently observed in both sexes across studies. In monkeys, no adverse effects on the ECG and other indicators of cardiac function were observed.

As indicated above, homocysteine levels were comparable in elafibranor- and placebo-treated NASH patients with and without MACE. In additional analyses, elafibranor was not associated with an increased risk of MACE in NASH patients. Homocysteine levels have not been evaluated in the clinical studies on PBC. For this reason, the clinical relevance of potentially increased homocysteine levels with respect to MACE in PBC patients is unknown.

Vital signs and body weight

In studies 319-1 and 216-1 no clinically relevant differences between treatment groups were observed for most vital sign parameters at baseline and after follow-up. This applies also to BMI evaluations.

Electrocardiograms

One elafibranor-treated participant in study 319-1 developed PR prolongation during follow-up. This event was considered possibly related to elafibranor treatment. However, similar observations were not obtained in other participants of study 319-1, and in study 216-1.

A TQT study in healthy volunteers (study GFT505-113-9) did not show any prolongation effect of elafibranor on QT interval at doses of 120 and 300 mg once daily for 14 days. No apparent effect of elafibranor on ECG morphology was observed. Different elafibranor and GFT1007 plasma concentrations had no impact on QT interval prolongation.

Aforementioned findings indicate that ECG changes due to elafibranor exposure are unlikely.

Ultrasonography

In study 319-1, no participants treated with elafibranor had abnormal, clinically significant liver or bladder ultrasound results at week 52.

Bone mineral density and serum bone markers

In study 319-1, there was no significant difference in the change in bone mineral density (g/cm^2) from baseline between elafibranor and placebo. No significant differences between these treatment groups were noted for increases in CTX (a marker for osteoclast activity and bone resorption) or in decreases in P1NP (a marker or osteoblast activity and bone formation). However, in the hip region an increase in T-score from baseline was noted for the elafibranor treated group compared to placebo (LS mean difference with placebo was 0.325 (95% CI: 0.056; 0.595; p=0.0186) in contrast with other regions in which no differences in changes in T-scores from baseline were observed between treatment groups. The applicant explained later that the deviant result with respect to the hip bone mineral density is probably explained by the relatively high T-score for placebo and a trend for a higher decrease in T-scores for placebo treatment at week 52 in the hip region as compared to the femoral neck and lumbar bone mineral densities for placebo treatment at baseline and week 52. The bone mineral density remained stable during elafibranor treatment in different hip and lumbar bone regions. Because of this consistent trend across different bone regions, the observed deviant result with respect to the total hip bone mineral density as compared to the femoral neck and lumbar bone mineral density is not considered clinically relevant.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

See also discussion under Additional efficacy data needed in the context of a conditional marketing authorisation.

The number of PBC patients who were exposed to elafibranor is limited (n= 206). Since elafibranor is a first in class drug, it is not possible to rely fully on the additional data provided on the safety profile of elafibranor in other indications. The long-term safety profile of elafibranor is yet unknown. Long-term safety data may provide additional insight into its tolerability and safety profile including hepatic and renal function and its target selectivity. Long-term safety, hepatic safety and myopathy including

rhabdomyolisis for elafibranor will be followed up by means of the agreed specific obligation and with additional pharmacovigilance measures as defined in the risk management plan.

2.6.10. Conclusions on the clinical safety

Limited safety data are available in PBC patients. 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. The long-term safety profile of elafibranor in PBC patients is yet unknown.

Overall, the short-term safety profile of elafibranor appears manageable. Gastro-intestinal events were the most commonly reported adverse drug reaction for which a relevant difference compared to placebo was observed. From the safety characterisation, elafibranor might be associated with a higher risk of liver events and myopathies although no clear causal relationship can be established at present. Both risks are followed up by additional pharmacovigilance measures and are defined potential risks in the RMP. Furthermore, the SmPC advises to perform clinical and laboratory assessment of liver function prior to initiation of elafibranor treatment and thereafter according to routine patient management. If increases in liver biochemical tests and/or liver dysfunction are observed, prompt investigation of the cause is recommended and interruption of elafibranor treatment should be considered. In addition, a higher risk of increased creatine levels has been observed. However, data supporting a causative role are scarce. Blood creatinine increased is labelled in SmPC 4.8 with an uncommon frequency. The safety profile of elafibranor in PBC patients was comparable to that of elafibranor with respect to data generated in other (non-approved) indications.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

Description	**Due date**
In order to confirm the efficacy and safety of elafibranor in 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, the MAH shall conduct and submit the final results of the phase III randomised, parallel-group, double-blind, placebo-controlled, two-arm study (ELFIDENCE) to evaluate the efficacy and safety of elafibranor on long-term clinical outcomes in adults with Primary biliary cholangitis (PBC).	May 2030

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 36: Summary of safety concerns

Important identified risks	None
Important potential risks	• Hepatic events • Myopathy including rhabdomyolysis
Missing information	Long-term safety

2.7.2. Pharmacovigilance plan

Table 37: Summary of ongoing and planned additional PhV activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Phase III Study (CLIN-60190-454) A Phase III Randomised, Parallel-Group, Double-Blind, Placebo-Controlled, Two-Arm Study to Evaluate the Efficacy and Safety of Elafibranor 80 mg on Long-Term Clinical Outcomes in Adult Participants with Primary Biliary Cholangitis (PBC) (Ongoing)	The objective of this confirmatory phase III study is to confirm the efficacy and safety of elafibranor to convert the conditional approval into a standard marketing authorisation and to evaluate the long-term clinical outcomes and long-term safety of elafibranor 80 mg in participants with PBC and cirrhosis.	• Hepatic events • Myopathy including rhabdomyolysis • Long term safety	Protocol submission	29 September 2023 (actual date)
			Interim reports:	Interim analyses depend on adjudicated clinical outcome events; therefore, dates cannot be provided at this moment
			Planned Final report	May 2030
Category 3 - Required additional pharmacovigilance activities				
Phase III Study (GFT505B-319-1) A Double-blind, Randomised, Placebo-Controlled Study and Open-label Long-Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid. (DBP: Completed; LTE period-Ongoing)	The objective of the second part of this study (ie, open-label LTE period) is to evaluate the effect of elafibranor (80 mg/day) during the LTE period on safety and tolerability, and on maintenance of efficacy from the DB period.	• Hepatic events • Myopathy including rhabdomyolysis • Long-term safety	Protocol submission	17 August 2020 (actual date)
			Planned Final report	November 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Phase IV Study (CLIN-60190-461) Prospective Non-Interventional, Phase IV Multicentre Study to Assess the Effectiveness, Safety and Tolerability of Elafibranor 80 mg/day in Patients with Primary Biliary Cholangitis Receiving Treatment in a Real-World Setting. (Planned)	The aim of this study is to evaluate patients with PBC, for whom the treating physician has decided to start treatment with elafibranor 80 mg/day as recommended in the approved indication, over a period of 24 months to assess effectiveness and safety of elafibranor and its impact on patients' QoL.	• Hepatic events • Myopathy including rhabdomyolysis • Long-term safety	Planned Protocol submission	09 April 2024
			Interim reports	The first interim analysis will be planned when 50 patients have completed their three months of treatment with elafibranor (80 mg/day). Therefore, dates cannot be provided at this moment.
			Planned final report	December 2032

DBP=double -blind period; LTE=long term- extension; PBC=primary biliary cholangitis; QoL=quality of life.

2.7.3. Risk minimisation measures

Table 38: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hepatic events	Routine risk communication: EU SmPC Section 4.4: Special warnings and precautions for use Package leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: EU SmPC Section 4.4 includes recommendations for clinical and laboratory assessment of liver function prior to initiation of elafibranor treatment and thereafter according to routine patient management. This is also reflected in package leaflet Section 2. Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine.
Myopathy including rhabdomyolysis	Routine risk communication: EU SmPC Section 4.4: Special warnings and precautions for use Package leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: EU SmPC Section 4.4 includes recommendations for evaluating CPK prior to initiation of elafibranor treatment and thereafter according to routine patient management, with periodic CPK measurements to be considered

	in patients starting elafibranor treatment, especially those on concomitant HMG-CoA reductase inhibitors (statins). This is also reflected in package leaflet Section 2. Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine.
Missing Information: Long-term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 10 June 2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has

been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The volume of the container is bigger than the 10-ml limit to qualify for small immediate packaging (40 ml HDPE bottle). Due to technical labelling issues at the packaging site, the applicant had to develop a 95 mm bottle label to meet quality compliance criteria; however, this 95 mm bottle label didn't allow for applying the full particulars without affecting overall readability of the label.

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The applicant was seeking an exemption under Article 63(1), proposing that the details listed in Article 54 appear in only one official language (English) on the outer carton and the bottle label for the following EU Member States: Bulgaria, Croatia, Cyprus, Czechia, Estonia, Greece, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia.

The applicant considered that these proposals were justified on the basis:

- Orphan medicinal product and limited production volumes/forecasts or this unmet medical need. The applicant estimates PBC prevalence ranging between 1.15 to 3.83 per 10 000 people in the EU. Low prevalence of PBC and low forecasted volume numbers (less than 70 packs/year) are estimated in the EU countries listed above.
- Considering the low and very heterogeneous sales volumes across the different European markets, the use of English language only for the outer carton and the bottle label will streamline the manufacturing process and distribution efficiency by improving the reactivity of production and enabling faster delivery of the medicine to patients. This results in a significant reduction in waste per country for both bottle and carton labels, while optimising the use of product shelf-life and reducing the manufacturing costs by minimising the need for different batches of packaging.

The applicant claimed that having English packs for these countries will not compromise patient safety since the patient information leaflet, which contains key safety information, will be provided in the local language(s) of each Member State listed above.

Outcome: The proposal was found acceptable by the following Member States, provided that the package leaflet and national specific information (i.e. blue box) are provided in the national languages: Bulgaria, Croatia, Estonia, Greece, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia.

For Cyprus, the MAH should contact the Cyprus NCA to finalise the decision.

Czech Republic would accept this translation exemption until the end 2026. For a further extension, the MAH should contact the relevant NCA.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Iqirvo (elafibranor) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed therapeutic indication is:

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.*

Primary biliary cholangitis (PBC) is an autoimmune disease of the liver. It results from a slow, progressive destruction of the small bile ducts of the liver, causing bile and other toxins to build up in the liver (cholestasis), leading to liver fibrosis and ultimately cirrhosis.

At the time of diagnosis, a considerable part of the patients are in the earliest stage of disease and do not experience symptoms yet. As the disease progresses, common symptoms are tiredness, itching, and in more advanced stages, jaundice and other signs and symptoms of liver failure. In late stage PBC, patients may develop progressive jaundice, portal hypertension, and liver failure, and progress to liver-related death in the absence of liver transplant.

PBC is a relatively rare disease, affecting up to one in 3,000–4,000 people in the European Union. It is much more common in women, with a sex ratio of at about 9:1 female to male.

The goal of the treatment with elafibranor is to establish a delay in the ongoing deterioration or conservation of the liver function. It can therefore be considered as a disease modifying treatment. Currently the measurement of ALP and TB together with other tests are established to monitor liver deterioration. Long term studies are needed to confirm a clinically relevant benefit.

3.1.2. Available therapies and unmet medical need

The only approved medical therapies in Europe for the treatment of PBC are UDCA, a hydrophilic, noncytotoxic bile acid and obeticholic acid (OCA, Ocaliva) a semi-synthetic analogue of the primary bile acid chenodeoxycholic acid, which selectively activates the nuclear hormone receptor farnesoid X receptor.

Despite the availability of approved medical therapies for PBC, there is a clear unmet need for additional therapies given the considerable percentage of non-responders to UDCA (up to 40% of patients is reported to have a treatment failure) at high risk of progression to end stage liver disease, and the limited therapies available to treat the symptoms of pruritus and fatigue that have a major impact on patient QoL. The only treatment authorised in second line is Ocaliva (obeticholic acid) which, unlike Iqirvo (elafibranor), is contraindicated in this liver disease for the use in decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event. Ocaliva is currently authorised under a conditional marketing authorisation.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single Phase 3 multicentre, randomised, placebo-controlled study comparing elafibranor, 80 mg oral tablet once daily (n=108) vs. placebo (n=53) in adults with an inadequate response to UDCA, or in adults unable to tolerate UDCA.

The primary efficacy endpoint of the study was response to treatment at Week 52 defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%.

3.2. Favourable effects

The primary endpoint on the pivotal study was the response to treatment based on cholestasis response at week 52 (defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%). Participants who prematurely discontinued the study treatment (intercurrent event, ICE-1) or used rescue therapy for PBC (ICE-2) prior to Week 52 were considered as non-responders. In the ITT population, at Week 52, the proportion of responders was 55/108 (50.9%) participants in the elafibranor group compared with 2/53 (3.8%) participants in the placebo group, resulting in an estimated difference of 47.2% (95% CI: 32.0; 56.9) favouring the elafibranor group. The primary analysis was confirmed by various supplemental analyses.

The proportion of responders to treatment based on ALP normalisation was greater in the elafibranor group (16/108 [14.8%] participants) than in the placebo group (0/53 [0.0%] participants) at week 52, resulting in an estimated difference of 14.8% (95% CI: 6.1; 22.7) favouring the elafibranor group.

The second and third key secondary endpoints, aimed at evaluating improvement of pruritus, a common symptom in PBC, were measured as a change from baseline in pruritus through week 52 and week 24. The analysis was conducted in the Pruritus ITT Analysis Set (n=44 elafibranor vs 22 placebo) in patients with moderate to severe pruritus, with a baseline PBC Worst Itch NRS score ≥4. Results did not reach the statistical significance, although a trend in decrease from baseline in the PBC Worst Itch NRS score was observed in the elafibranor group (-1.9; 95%CI -2.6, -1.3) compared with placebo (-1.2; 95%CI -2.1, -0.2). Similar results were observed at week 24 and in the ITT analysis set. Supplementary analyses using the PBC Worst Itch NRS as well as the 5D Itch Total score were similar.

Other secondary endpoints descriptively evaluating the biochemical response in elafibranor treated patients as compared to PLB according to different definitions showed results favouring elafibranor versus PLB when using different percentage cut-offs of ALP (alone) reduction at week 52: ALP reduction ≥10% (75.5% vs 22.6%), ≥20% (69.8% vs 5.7%), and ≥40% (54.7% vs 0%). Using a more stringent response than the primary endpoint (composite: ALP <1.5xULN, ALP decrease from baseline ≥40% and TB ≤ULN), response to treatment was achieved in 38% of participant receiving elafibranor and 0% in placebo.

Concerning hepatic biochemical measures of response including total bilirubin (TB), the other component of the primary composite endpoint, measured according to different definitions (TB ≤ULN and/or ALB ≥LLN, a 15% decrease in TB from baseline, TB ≤0.6 ULN, TB ≤ULN or no increase from baseline >0.1xULN), comparable results were observed in the treatment and placebo groups. Thus, TB was mainly unaffected by elafibranor treatment (change from baseline: -0.12 umol/L vs 1.14 in placebo).

Several composite endpoints including ALP and TB have been evaluated, with different cut-offs with respect to the primary endpoint; overall, the trend was in favour of elafibranor versus placebo. However, results are mainly driven by the effect on ALP since basal bilirubin levels were within normal ranges in the vast majority of patients.

An exploratory analysis was conducted to evaluate changes in fibrosis (Nakanuma score) in patients with available liver biopsy (35 paired biopsies at baseline and week 52), showing no clear signs of effect.

A non-invasive measurement of liver fibrosis by ELF (panel of 3 serum biomarkers giving a score reflecting severity of liver fibrosis) was not significantly different between the two arms.

A variety of PRO measures were evaluated: a slight improvement in elafibranor treated patients was shown for PROMIS Fatigue SF 7a questionnaire.

Subgroup analyses were performed for primary and key secondary endpoints, with results generally consistent with the primary analysis.

3.3. Uncertainties and limitations about favourable effects

The prognostic value of a biochemical response at Week 52, defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15% is not fully demonstrated. Changes in ALP and TB are used in clinical practice to inform on treatment choices as it is strongly suggested from literature that increases of these parameters are associated with a poorer clinical outcome. However, liver biomarkers are not validated surrogate endpoints for survival with native liver (SNL). In the absence of a validated surrogate biomarker, ALP and TB are included in the EMA reflection paper on PBC as accepted primary endpoints for studies in the add-on setting to support a CMA.

In addition, normalisation of ALP (key secondary endpoint), which would be the optimal goal to achieve (although a clear predictive value on long term outcome is not established), is seen only in a limited subset of patients (roughly 15%). Furthermore, TB, a predictor of PBC progression relevant especially in advanced/at risk patients, was mainly unaffected by elafibranor treatment. This result could be expected since almost all patients had normal baseline TB levels. However, both observations lead to the need for confirmatory data based on clinical endpoints as requested in this conditional marketing authorisation.

In exploratory analysis an improvement in fibrosis score (Nakanuma) was seen in 7/25 (28.0%) participants in the elafibranor group compared to 1/10 (10%) in the placebo group. There was no change in fibrosis score in 11/25 (44.0%) participants in the elafibranor group and 9/10 (90.0%) participants in the placebo group. Overall, interpretation of score shifts is hampered by the very limited number of patients tested and thus no effect on fibrosis could be inferred at this point. Moreover, a non-invasive measurement of liver fibrosis by ELF (panel of 3 serum biomarkers giving a score reflecting severity of liver fibrosis) was not significantly different between the two arms. Due to the slow progression of PBC, longer exposure to the drug and more patients undergoing to fibrosis assessment will be necessary post authorisation.

Only few data on relevant clinical outcomes are submitted within the present MAA; a total of 3 clinical events in 2 elafibranor participants occurred within 52 weeks of treatment (MELD Na >14, Uncontrolled ascites requiring treatment, Death). Other four participants had events (1 in the elafibranor and 3 in the placebo group), between Week 52 and up to Week 104. The numbers are very few to draw any conclusions, and the results on the long-term clinical outcomes defining the real benefit of a drug used in PBC treatment are still necessary to confirm elafibranor efficacy post authorisation.

Whilst efficacy data is mainly based on biochemical response it is observed that a more pronounced effect on liver biochemistry is observed in less advanced patients compared to more severely ill patients. As such the confirmation on long term clinical outcomes is needed also on advanced patients.

The second and third key secondary endpoints of the pivotal study were aimed at evaluating improvement of pruritus, a common symptom in PBC, measured as a change from baseline in pruritus through Week 52 and Week 24. The analysis was conducted in the Pruritus ITT Analysis Set (n=44 elafibranor vs 22 placebo) who had moderate to severe pruritus with a baseline PBC Worst Itch NRS score ≥4 (mean±SD baseline score of 6.2±1.50 and 6.3±1.15). Results did not reach the statistical significance, although a trend in decrease from baseline in the PBC Worst Itch NRS score was observed in the elafibranor group (-1.9; 95%CI -2.6, -1.3) compared with placebo (-1.1; 95%CI -2.1, -0.2). Similar results were observed at Week 24 and also in the ITT analysis set.

Supplementary analyses evaluating the proportion of participants achieving at least 1-point, 2-points, or 3-points decrease in PBC Worst Itch NRS score from baseline at week 24 and 52 were consistent with this trend. Results from analysis of the 5D Itch Total score were similar.

Thus, in summary, there seems to be a trend towards pruritus improvement, but of modest entity at best and the clinical relevance of this effect is not considered established.

The clinically relevant endpoints being metabolic decompensation, liver transplantation or death are not evaluated in these short-term (from the perspective of PBC development) studies. Due to this uncertainty a SOB (ELFIDENCE study) has been imposed, to confirm the clinical benefit and to provide comprehensive efficacy data. To address uncertainties about the feasibility of this study the ELFIDENCE study design has been modified.

The analysis based on the PBC Risk Scores (UKPBC and to GLOBE) reported at 15 years a median estimated difference in transplant-free survival rates of very limited magnitude (less than 5%); therefore, the potential impact of the drug on the risk remains to be demonstrated and to be confirmed by observed long-term outcomes.

The applicant is claiming elafibranor indication also as monotherapy in PBC patients unable to tolerate UCDA based on data coming from only 8 patients (6 received elafibranor and 2 placebo) enrolled in study 319-1. For only 4 out of 6 patients are data available at the end of the study: in three of these, an ALP reduction was observed (ranging from –90 to –182 U/L) but only one was considered responder based on the endpoint definition, whereas in the other patient an increase of 215 U/L was seen. No additional data or studies using elafibranor in monotherapy have been submitted. The rarity of the disorder and the even greater rarity of UDCA intolerance (estimated 3-5% of patients, from literature) it is however acknowledged and further data on monotherapy will be generated post authorisation. Importantly, in PBC patients not tolerating UDCA a high unmet need is recognised.

3.4. Unfavourable effects

The safety data set, although limited, is considered acceptable considering the rarity of PBC (affecting up to one in 3,000–4,000 people).

Overall, the short-term safety profile of elafibranor appears manageable. In study 319-1, treatment-emergent adverse events reported in ≥5% of participants in the elafibranor group and with a higher incidence than the placebo group (difference >1%) were mostly gastrointestinal in nature, including vomiting (11.1 versus 1.9%), diarrhoea (11.1 versus 9.4%), nausea (11.1 versus 5.7%), constipation (8.3 versus 1.9%), abdominal pain upper (7.4 versus 5.7%), and gastroesophageal reflux disease (6.5 versus 1.9%). Gastrointestinal adverse reactions are labelled in the SmPC as very common.

From the safety characterisation, elafibranor might be associated with a higher risk of liver events and myopathies although no clear causal relationship can be established at present. Both risks are followed up by additional pharmacovigilance measures and are defined important potential risks in the RMP. Furthermore, the SmPC advises to perform clinical and laboratory assessment of liver function prior to

initiation of elafibranor treatment and thereafter according to routine patient management. If increases in liver biochemical tests and/or liver dysfunction are observed, prompt investigation of the cause is recommended and interruption of elafibranor treatment should be considered. In addition, a higher risk of increased creatine levels has been observed. However, data supporting a causative role are scarce. Blood creatinine increased is labelled in SmPC 4.8 with an uncommon frequency.

Elafibranor has shown evidence of developmental toxicity in both rats and rabbits. In rat pre- and post-natal study, maternal exposures to elafibranor (at or above 2-fold the AUC exposure at the maximum human recommended dose (MHRD)) led to reduced pup survival, developmental delay, or thrombosis. In pregnant rabbits, maternal exposure (3-fold the AUC exposure at MHRD) to elafibranor caused marked maternal toxicity, increased embryo-lethality, reduced foetal weight and a low incidence of foetal malformations. Accordingly, elafibranor is contraindicated in known or suspected pregnancy and in women of childbearing age who do not use contraception.

3.5. Uncertainties and limitations about unfavourable effects

The number of PBC patients who were exposed to elafibranor is limited (n= 206). Considering PBC is a rare disease with prevalence estimates ranging from 1.9 to 40.2 cases per 100,000 persons[2], and also that the total exposure to elafibranor for PBC and other conditions is in line with ICH E1 guidance (1994), the total elafibranor exposure to PBC and other conditions is however appropriate to weigh the benefits and risks of elafibranor treatment in current conditional marketing authorisation application of elafibranor for PBC.

Exposure data up to one year have been submitted in current marketing authorisation application. The follow-up period of the Phase 2 PBC study 216-1 was 12 weeks. The follow-up period of the Phase 3 PBC study 319-1 was 52 weeks until the data cut-off point. Accordingly, the long-term clinical safety of elafibranor treatment in PBC patients is yet unknown and will be complemented post authorisation by additional pharmacovigilance measures as described in the RMP.

Because of the limited number of included patients in the Phase 2 and 3 studies on PBC, and because of the limited observation time in these studies, there is an increased risk of chance findings. In addition, rare treatment-emergent adverse events will unlikely have been reported in aforementioned studies. It is not possible to extrapolate the safety profile of elafibranor from other conditions, since elafibranor has not been authorised for other indications.

In pivotal study 319-1, CPK elevations have been reported in 4 study participants, 3 out of 4 assessed as possibly related to study treatment. One case was associated to renal injury. A clear understanding of these events, including risk factors such as concomitant disease (e.g. autoimmune thyroiditis, chronic kidney disease) or concomitant medications (e.g. statins) known to be associated with CPK elevations is lacking. Myopathy including rhabdomyolysis is followed up as an important potential risk withing the RMP. SmPC Section 4.4 includes recommendations for evaluating CPK prior to initiation of elafibranor treatment and thereafter according to routine patient management, with periodic CPK measurements to be considered in patients starting elafibranor treatment, especially those on concomitant HMG-CoA reductase inhibitors (statins).

In study 319-1, hepatobiliary disorders tended to be reported more frequently among elafibranor-treated participants as compared to placebo-treated participants (7.4 vs. 1.9% respectively), in particular cholelithiasis (n=3 vs. 0). Three study patients met the pre-specified laboratory criteria for

[2] Floreani et al. Prevalence of familial disease in primary biliary cirrhosis in Italy. Journal of Hepatology. Volume 26, Issue 3, March 1997, pages 737-738.

drug-induced liver injury (DILI), one in the elafibranor group and two in the placebo group. According to the clinical events committee, DILI was possible in the elafibranor-treated study patient, and probably in the two placebo-treated study patients. Hepatic events are followed up within the RMP as an important potential risk. Cholelithiasis is labelled as a common adverse reaction in the SmPC and 4.4 of the SmPC includes as a precaution for use the advice to perform clinical and laboratory assessment of liver function prior to initiation of elafibranor treatment and thereafter according to routine patient management. If increases in liver biochemical tests and/or liver dysfunction are observed, prompt investigation of the cause is recommended and interruption of elafibranor treatment should be considered.

3.6. Effects Table

Table 39: Effects Table for Iqirvo 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. (based on Pivotal study (319-1) with data cut-off: 01 June 2023).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
			Elafibranor 80 mg once daily	Placebo once daily	
			n=108	n=53	
Favourable Effects					
Cholestasis responders at Week 52	ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%	% (95% CI)	50.9% (0.416; 0.602)	3.8 (0.010; 0.128)	The prognostic value of this endpoint for Iqirvo remains to be confirmed
responder ALP normalisation at Week 52	ALP normalisation	% (95% CI)	14.8% (0.093; 0.227)	0 (0.000; 0.068)	The prognostic value of this endpoint for Iqirvo remains to be confirmed
PBC Worst Itch NRS Score	PBC Worst Itch NRS Score at week 52 compared to baseline	LS means (95% CI)	-1.9 (-2.6; -1.3)	-1.2 (-2.1; -0.2)	Additional pruritic measures further support the results obtained with the PBC Worst Itch NRS Score
Unfavourable Effects					
TEAEs reported in ≥5% of participants in the elafibranor group and with a higher incidence than the placebo group (difference >1%)	Mostly mild to moderate gastrointestinal events vomiting diarrhoea nausea constipation abdominal pain upper gastroesophageal reflux disease	%	 11.1 11.1 11.1 8.3 7.4 6.5	 1.9 9.4 5.7 1.9 5.7 1.9	Safety profile elafibranor PBC in line with that of other conditions
Increased serum creatine levels	Proportion of study patients who had increased mean serum creatinine levels at week 52 with normal mean serum creatinine levels at baseline	%	14.6	6.7	Only scarce data available. Direct effects of elafibranor on renal function cannot be excluded at present. According to the applicant due to an increase in metabolic production of creatinine due to PPAR agonism.

Abbreviations: KDIGO: Kidney Disease Improving Global Outcomes, TEAE: treatment-emergent adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Currently, the primary endpoint of cholestasis response in Study 319-1, defined as an ALP <1.67 x ULN and TB ≤ULN and ALP decreased ≥15%, is recognised as a relevant marker for monitoring the treatment effect of PBC in clinical practice. In the pivotal study, clear statistically significant effects were demonstrated. A trend favouring elafibranor is demonstrated by other secondary endpoints. The magnitude of the effect can be considered as meaningful, however, the clinical relevance of such changes i.e. whether changes in biomarkers would translate into favourable clinical outcomes on the long-term is unclear.

Moreover, the treatment effects on the bilirubin component or on subgroups defining a more advanced/at risk population seems to be of less magnitude. The analysis based on the PBC Risk Scores (UK-PBC Score and GLOBE Score) suggest a limited effect on estimated transplant-free survival. Fibrosis related analysis (biomarkers for fibrosis, fibro-scan and histology) show some improvement. However, the clinical relevance of these improvements remains to be established. It is further acknowledged that 52 weeks treatment might be too short for the full appreciation of the clinical relevance.

The observed effects on pruritus, sleep and QoL are nor statistically significant nor clinically relevant. Additional analyses support these findings and conclusions.

The use of elafibranor in monotherapy in patients not tolerant to UCDA represents the subset with the highest unmet need. Whilst limited data are available and confirmation post-authorisation is needed, similar effects are expected based on biological plausibility.

A limited number of PBC patients (n= 206) have been included in the conducted Phase 2 and 3 clinical studies on elafibranor. Although some uncertainties are identified in general with respect to the safety profile of elafibranor in PBC patients specifically on the occurrence of hepatic events and myopathy including rhabdomyolysis which are followed up upon as important potential risks in the RMP, the overall safety profile of elafibranor is considered mild with most of the adverse event of mild to moderate severity.

Pre-clinical studies showed that treatment of pregnant female rodents with peroxisome proliferator-activated receptor alpha (PPAR-alpha) agonists results in notable effects on the ability to maintain a healthy pregnancy and foetal development. Similar observations were obtained in humans with other conditions than PBC (e.g. NASH). The risk of developing embryofoetal abnormalities is also considered relevant for PBC patients because of aforementioned safety risks and to prevent further harm, although embryofoetal abnormalities have, thus far, not been observed in human PBC patients. Therefore, the use of elafibranor is contraindicated in known or suspected pregnancy and in women of childbearing age who do not use contraception.

The available safety data set is limited but acceptable for a rare condition as PBC. Overall, comparable short-term safety risks of elafibranor were observed in PBC and other conditions (e.g. NASH, NAFLD). This supports the relevance of the observed short-term safety profile of elafibranor in the study population of PBC patients. The safety profile of elafibranor is considered overall manageable and long-term safety is followed up as described in the RMP.

3.7.2. Balance of benefits and risks

After 52 weeks of treatment, Iqirvo (elafibranor) demonstrated to be effective in improving most of the biomarkers used to monitor treatment response in PBC and accepted as surrogate parameters with a reasonable likelihood to translate into clinically relevant outcomes and in the pivotal study clearly statistically significant effects were shown. The magnitude of the effect can be considered as clinically meaningful, however, whether changes in biomarkers would translate into favourable clinical outcomes on the long-term for elafibranor still needs to be confirmed. A trend favouring elafibranor was also demonstrated by other secondary endpoints.

The liver fibrosis related measurements (biomarkers for fibrosis, fibro-scan and histology) as well as the prognostic models for the risk of liver transplantation (UK-PBC and Global PBC score) do show some improvement albeit not clinically relevant. The effect on clinical symptoms, i.e. pruritus, appear to show a trend but results are not considered clinically relevant.

The primary endpoint of cholestasis response in Study 319-1 was defined as an ALP <1.67 x ULN and TB ≤ULN and ALP decreased ≥15%. At present, it has only been demonstrated for the natural history, as well as for UDCA, that the reduction of ALP and bilirubin leads to an overall improved outcome with regard to the development of end-stage liver disease, decompensation, liver transplantation and death. Whilst this endpoint and the provided data can be considered to translate with reasonable likelihood into clinically relevant outcomes confirmatory efficacy data is needed post-authorisation based on imposed conditions.

The safety profile of elafibranor based on the data provided is considered overall manageable. It consists mainly of mild to moderate adverse events, often of gastro-intestinal origin. Based on data from animal studies elafibranor is suspected to cause congenital malformations and reduced foetal survival when administered to a pregnant woman. But this risk is considered balanced with a contra-indication in women with a known or suspected pregnancy and in women of childbearing age who do not use contraception.

As the data provided in this marketing authorisation application is not considered comprehensive (efficacy is based on biochemical surrogate parameters i.e. no comprehensive data on clinically relevant endpoints were provided and the long-term safety profile of elafibranor is unknown), the applicant applies for a conditional marketing authorisation. Study CLIN-60190-454 is requested as a commitment to fulfil the conditions of the marketing authorisation (Specific Obligation). This is a Phase III Randomised, Parallel-Group, Double-Blind, Placebo-Controlled, Two-Arm Study to Evaluate the Efficacy and Safety of elafibranor 80 mg on Long-Term Clinical Outcomes in Adult Participants with Primary Biliary Cholangitis (PBC). The aim of this study is to confirm the efficacy and safety of elafibranor in the applied indication based on long-term clinical outcomes.

These studies, when completed, are considered suitable to confirm the clinical relevance of the treatment effect with elafibranor.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and life-threatening disease.

Primary biliary cholangitis is a rare, chronic, progressive autoimmune cholestatic liver disease characterised by lymphocytic cholangitis and intralobular bile duct destruction leading to development of fibrosis, cirrhosis, and liver failure that impacts quality of life (QoL) and is associated with increased mortality [Hirschfield 2013]. If left untreated, survival of patients with PBC is significantly lower than that of the general population due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Therefore, PBC is considered a seriously debilitating and life-threatening disease. Furthermore pruritus, fatigue and abdominal pain are the main symptoms of the disease.

Current treatment options are limited. The only approved medical therapies in Europe for the treatment of PBC are UDCA (first line) and Obeticholic acid (second line, approved under conditional marketing authorisation). Ocaliva is contraindicated in advanced stages of the disease (e.g. in patients with moderate (Child-Pugh B) hepatic impairment.

The application applied for Iqirvo (elafibranor) as second line treatment i.e. in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.

In addition, the product is designated as an orphan medicinal product.

The CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

The provided efficacy data are mainly based on results of the primary endpoint that 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%, that, although not validated, is an intermediate measure of effect used in the PBC setting with a reasonable likelihood to translate into clinically relevant outcomes. The actual clinical relevance of this endpoint and the predictive value on clinical benefit for elafibranor remains however to be confirmed. The data provided on biochemical response in the monotherapy setting is considered particularly sparse, but the rarity of the disorder and the even greater rarity of UDCA intolerance (estimated 3-5% of patients) is acknowledged.

Only few data on relevant clinical outcomes are submitted within the present MAA; a total of 3 clinical events in 2 elafibranor participants occurred within 52 weeks of treatment (MELD Na >14, Uncontrolled ascites requiring treatment, Death). Other four participants had events (1 in the elafibranor and 3 in the placebo group), between Week 52 and up to Week 104. The numbers are very few to draw conclusions, and the results on the long-term clinical outcomes defining the real benefit of a drug used in PBC treatment are still necessary to confirm elafibranor efficacy post authorisation.

The number of PBC patients who were exposed to elafibranor is limited (n= 206). Since elafibranor is a first in class drug, it is not possible to rely fully on the data provided on the safety profile of elafibranor in other non-authorised indications as provided. The long-term safety profile of elafibranor in the treatment of PBC is yet unknown. Long-term safety data may provide additional insight into its tolerability and safety profile including hepatic and renal function and its target selectivity. Long-term safety, hepatic safety and myopathy including rhabdomyolisis for elafibranor will be followed up post-authorisation in order to establish comprehensive data on elafibranor in the indication 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.

For this purpose, the applicant will submit post-authorisation the result of the ongoing phase III, randomised, parallel-group, double-blind, placebo-controlled, multicentre, event-driven study to confirm the efficacy and safety of elafibranor 80 mg/day in the agreed indication (study 454; EU CT:

2023-505251-43-00) including also PBC patients with more advanced disease and in the monotherapy setting.

The primary endpoint of this study, meant to provide confirmatory evidence based on clinical outcomes, is: event-free survival, as time to the first occurrence of any of the following: all-cause mortality, liver transplant, liver decompensation, change in MELD-Na score to ≥15, development of hepatocellular carcinoma; the primary endpoint and the clinical events chosen are deemed appropriate to gather significant clinical information on the efficacy of elafibranor. Other endpoints will evaluate progression to cirrhosis, changes in biochemical markers, including the surrogate endpoints used in the data already provided.

Apart from identifying countries with no or limited access to alternative second-line treatments for PBC to run the study, the applicant agreed to amendments to the protocol during the procedure in order to improve the study design to meet better the purpose of providing confirmatory data such as:

1. Change in randomisation ratio to 1:1.

2. Modification of the primary composite endpoint to only include established clinical outcome events.

3. Updates to the inclusion/exclusion criteria to enrol a population with more advanced PBC to decrease heterogeneity in the study population and further improve feasibility by lessening the expected time to onset of a clinical outcome event.

The CHMP will be provided with annual updates within annual renewal applications.

- Unmet medical needs will be addressed,

  There are two authorised medicinal products in the EU for the treatment of PBC: ursodeoxycholic acid (first line) and Ocaliva (second line). Despite the availability of approved medical therapies for PBC, there is an unmet need for additional therapies given the large percentage of non-responders to UDCA at high risk of progression to end stage liver disease, and the limited therapies available to treat the symptoms of pruritus and fatigue that have a major impact on patient QoL. Up to 40% of patients treated with UDCA have an inadequate response [Murillo Perez 2023] and such patients remain at high risk of disease progression and have reduced transplant-free survival rates compared to those classified as UDCA responders [Lammers 2014, Kuiper 2009]. Iqirvo will be indicated as second line treatment to UDCA i.e. in in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. Ocaliva (authorised under conditional marketing authorisation) is the only existing second line treatment to UDCA with the same indication as applied for Iqirvo.

  However, Ocaliva is contra-indicated for PBC patients with decompensated cirrhosis (including progression to Child-Pugh Class B or C) or in patients with a prior decompensation event. Furthermore, according to section 4.4 of the SmPC (special warnings and precautions for use) treatment with Ocaliva should be permanently discontinued in patients with laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy), including progression to Child-Pugh Class B or C.

  For Iqirvo, based on the results from an open-label, phase 1, single dose study 118-14 after administration of elafibranor 120 mg in adults with hepatic impairment and healthy subjects, the total drug exposure of the parent and active metabolite was not significantly different between participants with normal hepatic function and hepatically impaired participants (Child Pugh A, B and C). The unbound fraction of elafibranor and its active metabolite increased by approximately 3-fold in the severe (Child Pugh C) hepatically impaired PBC participants. Therefore, Iqirvo is not

recommended for the use in patients with severe hepatic impairment (Child-Pugh C) but compared to Ocaliva, it can be used in a broader patient subset, which also includes patients with moderate (Child Pugh B) hepatic impairment and patients with a prior hepatic decompensation event. As PBC is a progressive liver disease Iqirvo will allow treatment of patients in later stages. Considering that UDCA non-responders with compensated cirrhosis appear to show a higher rate of hepatic decompensation (John, 2021) a medical need for second line treatment is evident in more advanced stages.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  The immediate availability of Iqirvo (elafibranor) allows for the treatment of patients who cannot be treated or are unable to tolerate or are unresponsive to both first- and second-line treatments currently authorised. Elafibranor is going to be indicated as second line to UDCA and currently the only second line treatment authorised for the treatment of PBC (Ocaliva) is contraindicated in patients in more advanced stages of the disease (e.g. Child-Pugh Class B; moderately severe liver disease). Iqirvo (elafibranor) in combination with UDCA or as monotherapy in patients unable to tolerate UDCA can be used in this patient population with a high risk of further disease progression. The known safety profile of Iqirvo is mild and manageable.

  Overall, the CHMP agrees that the benefits to public health of the immediate availability of Iqirvo (elafibranor) outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit/risk balance of Iqirvo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Iqirvo is not similar to Ocaliva within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Iqirvo is favourable in 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 patients unable to tolerate UDCA.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to confirm the efficacy and safety of elafibranor in 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, the MAH shall conduct and submit the final results of the phase III randomized, parallel-group, double-blind, placebo-controlled, two-arm study (ELFIDENCE) to evaluate the efficacy and safety of elafibranor on long-term clinical outcomes in adults with Primary Biliary Cholangitis (PBC).	May 2030

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Elafibranor is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.