EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP)

Active substance(s) (International Nonproprietary Name or common name)	Elafibranor (INN), IPN60190
Pharmacotherapeutic group (Anatomic Therapeutic Chemical (ATC) Code):	A05AX06
Name of Marketing Authorisation Holder (MAH) or Applicant:	Ipsen Pharma
Number of medicinal products to which this Risk Management Plan (RMP) refers:	One
Product(s) concerned (brand name(s)):	IQIRVO

Data lock point (DLP) for this RMP: 01 June 2023 (data cut-off date for the clinical study report [Double-Blind Period (DBP)]) for Study 319-1.

Version Number: 1.1

Date of final sign off: 03 June 2026

Rationale for submitting an updated RMP:

Update to the specific adverse reaction follow-up questionnaires included in the EU-RMP, namely for hepatic events and muscle injury. These updates are limited to the inclusion of administrative information (e.g. introductory text and data privacy statement), in alignment with the EMA Guideline on specific adverse reaction follow-up questionnaires.

Qualified Person for Pharmacovigilance (QPPV) name:

Frederique KORN

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation QPPV or their deputy. The electronic signature is available on file.

[redacted]

Administrative information on the Risk Management Plan

Table 1 Summary of Significant Changes in the RMP

Part	Module/Annex	Significant changes in this RMP
Part I **Product Overview**		Not applicable
Part II **Safety Specification**	**Module SI** Epidemiology of the Indication and Target Population(s)	Not applicable
	Module SII Nonclinical Part of the Safety Specification	Not applicable
	Module SIII Clinical Trial Exposure	Not applicable
	Module SIV Populations Not Studied in Clinical Trials	Not applicable
	Module SV Post-authorisation Experience	Not applicable
	Module SVI Additional European Union (EU) Requirements for the Safety Specification	Not applicable
	Module SVII Identified and Potential Risks	Not applicable
	Module SVIII Summary of the Safety Concerns	Not applicable
Part III Pharmacovigilance Plan (including post-authorisation studies)		Not applicable
Part IV Plans for Post-authorisation Efficacy Studies		Not applicable
Part V Risk Minimisation Measures		Not applicable
Part VI Summary of the RMP		Not applicable
Part VII Annexes	Annex 1 EudraVigilance Interface	Not applicable
	Annex 2 Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme	Not applicable
	Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Programme	Not applicable

Part	Module/Annex	Significant changes in this RMP
	Annex 4 Specific Adverse Drug Reaction Follow-Up Forms	Update to the specific adverse reaction follow-up questionnaires included in the EU-RMP, namely for hepatic events and muscle injury. These updates are limited to the inclusion of administrative information (e.g. introductory text and data privacy statement), in alignment with the EMA Guideline on specific adverse reaction follow-up questionnaires.
	Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV	Not applicable
	Annex 6 Details of proposed Additional Risk Minimisation Activities (if applicable)	Not applicable
	Annex 7 Other Supporting Data (including referenced material)	Not applicable
	Annex 8 Summary of Changes to the RMP Over Time	Not applicable

Other RMP versions under evaluation:

There are no other RMP versions under evaluation.

Details of the currently approved RMP:

Version number	1.0
Approved with procedure	EMEA/H/C/006231
Date of approval (opinion date)	25 July 2024

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LIST OF ABBREVIATIONS

Abbreviation	Wording definition
AE	Adverse event
ALP	Alkaline phosphatase
AMA	Anti-mitochondrial antibodies
ATC	Anatomic Therapeutic Chemical
CI	Confidence interval
C_{max}	Maximum plasma concentration
CREST	Calcinosis, Raynaud's, oesophageal dysfunction, sclerodactyly, and telangiectasias
CSR	Clinical study report
DBP	Double-blind period
dL	decilitre
DLP	Data Lock Point
EFD	Embryo-foetal development
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU QPPV	European Union Qualified Person for Pharmacovigilance
EU RMP	European Union Risk Management Plan
FEED	Fertility and early embryonic development
GVP	Good Pharmacovigilance Practices
h	Hour
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International Nonproprietary Name
LLNA	Local Lymph Node Assay
LOAEL	Lowest observed adverse effect level
LTE	Long-term extension
MAH	Marketing Authorisation Holder
mg	Milligram
mL	Millilitre
NA	Not applicable
NASH	Nonalcoholic steatohepatitis
NC	Not collected
ng	nanogram
NOAEL	No-observed adverse effect level
NRS	Numeric rating scale
PAK2	P21 activated kinase 2
PBC	Primary biliary cholangitis

Abbreviation	Wording definition
PDGFRα	Platelet-derived growth factor receptor alpha
PI	Prescribing information
PK	Pharmacokinetic
PND	Post-natal day
PPAR	Peroxisome proliferator-activated receptor
PPARα	Peroxisome proliferator-activated receptor alpha
PPARδ	Peroxisome proliferator-activated receptor-delta
PPARγ	Peroxisome proliferator-activated receptor-gamma
PPND	Pre- and post-natal development
PV	Pharmacovigilance
QoL	Quality of life
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TB	Total bilirubin
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
USPI	United States Prescribing Information

PART I: PRODUCT OVERVIEW

Table 2 Product(s) Overview

Active substance(s) (International Nonproprietary Name (INN) or common name)	Elafibranor (INN) IPN60190 (Ipsen code) GFT505 (Genfit code)
Pharmacotherapeutic group(s) (ATC Code)	A05AX06
Marketing Authorisation Applicant	Ipsen Pharma
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	IQIRVO
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Peroxisome proliferator-activated receptor (PPAR) α/δ agonist.
	Summary of mode of action Elafibranor and its main active metabolite GFT1007 are agonists of PPARα and PPARδ. Elafibranor activity is carried by both the parent drug and GFT1007, which respectively show a 3.8fold and a 5.4-fold selectivity for activation of human PPARα over human PPARδ. Activation of PPARα leads to a decrease in bile acid synthesis, an increase in bile acid transport into the canalicular space and increased detoxification of bile acids through increased uptake in micelles. Activation of PPARδ leads to beneficial effects on bile homeostasis, including decrease of hepatocyte bile acids synthesis and decrease of intestinal cholesterol (obligatory precursor of bile acids) absorption by stimulation of transintestinal cholesterol efflux. PPARα and PPARδ activation also has- -anti-inflammatory effects by acting on different pathways of inflammation (nuclear factor kappa B and B-cell lymphoma 6 pathways, respectively).
	Important information about its composition <u>Tablet content:</u> *Active substance:* Elafibranor *Excipients:* Microcrystalline cellulose (E460) Povidone (E1201) Croscarmellose sodium (E468) Anhydrous colloidal silica (E551) Magnesium stearate (E470b) <u>Film-coating:</u> Polyvinyl alcohol-part hydrolysed (E1203) Titanium dioxide (E171) Macrogol (PEG3350) (E1521) Talc (E553b) Iron oxide yellow (E172) Iron oxide red (E172)
Hyperlink to the Product Information	EU Summary of Product Characteristics (SmPC)

Indication(s) in the EEA	**Current:** Elafibranor is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA
	Proposed (if applicable): Not applicable
Dosage in the EEA	**Current:** 80 mg/day
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	**Current (if applicable):** Film-coated tablet, 80 mg
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC=Anatomical Therapeutic Chemical; EEA=European Economic Area; EU=European Union; INN=international nonproprietary name; mg=milligram; PBC=primary biliary cholangitis; PPAR=peroxisome proliferator-activated receptor; PPARα=peroxisome proliferator-activated receptor alpha; PPARδ=peroxisome proliferator-activated receptor-delta; RMP=risk management plan; SmPC=Summary of Product Characteristics; UDCA=ursodeoxycholic acid.

PART II: SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the Indication(s) and Target Population(s)

Primary biliary cholangitis

Incidence:

1.76 new cases per 100,000 person-years globally [Lv 2021]

1.87 new cases per 100,000 person-years in Europe [Gazda 2021]

2.75 new cases per 100,000 person-years in North America [Lv 2021]

0.84 new cases per 100,000 person-years in the Asian-Pacific region [Lv 2021]

Prevalence:

14.60 cases per 100,000 persons globally [Lv 2021]

22.27 cases per 100,000 persons in Europe [Gazda 2021]

21.81 cases per 100,000 persons in North America [Lv 2021]

9.82 cases per 100,000 persons in the Asian-Pacific region [Lv 2021]

Note: incidence and prevalence values reported above are pooled values generated by meta-analyses.

Demographics of the population in the proposed indication and risk factors for the disease:

Primary biliary cholangitis is a rare, chronic, progressive liver disease of autoimmune aetiology, characterised by injury of the intrahepatic bile ducts that, in untreated patients or non-responders to existing therapies, may progress to hepatic fibrosis, cirrhosis, hepatic decompensation, and death unless the patient receives a liver transplant [Kumagi 2008, Kuiper 2010, Hirschfield 2018].

The incidence of PBC appears to be greater in North America and Europe compared with the Asian -Pacific region, which could be either due to genetics or higher awareness of PBC in North America and Europe leading to more diagnoses [Lv 2021]. There is a strong female predominance of PBC with a reported female-to-male ratio of 9:1 [Galoosian 2020] in historical cohorts, although ratios as low as 4:1 have been reported in some recent population based studies [Colapietro 2022]. It is typically diagnosed in patients between 40 and 60 years of age, and global estimates suggest that 1 in 1,000 females aged >40 years are living with PBC [Lv 2021, EASL 2017].

Cumulatively, the risk of development of PBC is raised with a family history of the disease; a history of urinary infections, vaginal infections or smoking; comorbidity with other autoimmune diseases and previous pregnancies [Selmi 2011].

The main existing treatment options:

The only approved medical therapies in Europe for the treatment of PBC are ursodeoxycholic acid (UDCA), a hydrophilic, noncytotoxic bile acid [Shi 2006, UDCA SmPC] 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, Ocaliva SmPC]. Ursodeoxycholic acid (UDCA), which is an epimer of the primary human bile acid, chenodeoxycholic acid, was the first treatment for PBC approved by regulatory authorities. Treatment with UDCA at a dose of 13 to 15 mg/kg/day has been recommended as the first-line therapy for patients with PBC in the treatment guidelines of the European Association for the Study of the Liver [EASL 2017] and the American Association for the Study of Liver Diseases [Lindor 2019]. While UDCA has had a marked impact on clinical outcomes in PBC, a large proportion of patients have an inadequate response. It is estimated that up to 40% of UDCA-treated patients have a suboptimal response to UDCA, and that alkaline phosphatase (ALP) remains elevated in up to 70% of patients [Ali 2015, Lammers 2014]. Such patients remain at risk of disease progression and long-term adverse clinical outcomes.

More recently, obeticholic acid (Ocaliva®), a semi-synthetic analogue derived from the naturally occurring bile acid chenodeoxycholic acid which selectively activates the farnesoid X receptor (nuclear hormone receptor), was granted a Conditional Marketing Authorisation with the European Medicines Agency (EMA) as a second-line therapy "for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA". However, the efficacy of obeticholic acid as second-line therapy is incomplete, with less than half of patients treated with obeticholic acid, alone or in combination with UDCA, achieving biochemical response (ALP <1.67× the upper limit of normal (ULN) and ≥15% decrease from baseline and normal total bilirubin levels), and improvement in survival or disease-related symptoms has not yet been established [Nevens 2016]. Furthermore, liver-related adverse drug reactions, severe pruritus and reduction in high-density lipoprotein cholesterol have been reported with its use, and in June 2022 the EMA restricted the use of obeticholic acid in patients with PBC and cirrhosis of the liver after patients with PBC who took obeticholic acid developed hepatic decompensation and failure [Ocaliva SmPC].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Primary biliary cholangitis is characterised by chronic cholestasis, with progressive impairment of bile flow in the liver caused by autoimmune destruction of biliary ductules. This leads to increased hepatocellular bile acid levels which are toxic to the liver, causing injury of the intrahepatic bile ducts, which is associated with a local inflammatory response. This cholestatic injury results in elevated serum ALP concentrations, a hallmark of PBC [Hirschfield 2018]. The disease is suspected when patients present with prolonged cholestasis as indicated by persistent elevated ALP, in the absence of other liver diseases. In such adult patients with persistent cholestasis, a diagnosis of PBC is based on the presence of at least 2 of 3 of the following diagnostic criteria: an elevated serum ALP level (>1.5 times the 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]. Immunoglobulin M and AMA are immunological hallmarks of PBC, and AMA is a diagnostic marker of the disease present in approximately 90% of patients [Hirschfield 2013]. Current guidelines recommend against liver biopsy for the diagnosis of PBC, unless PBC-specific antibodies are absent, or there is a reason to suspect overlap with autoimmune hepatitis or other coexisting liver diseases, such as nonalcoholic steatohepatitis (NASH) [EASL 2017].

The natural history of untreated PBC comprises four phases: autoimmune response, bile build-up and inflammation, liver scarring (fibrosis), cirrhosis and end-stage liver disease. The first phase is a preclinical phase with AMA present in the serum but no liver enzyme abnormalities. An intermediate phase of PBC follows, where signs and symptoms of cholestasis develop, while underlying lesions progress to ductopenia and liver fibrosis; this phase can continue for up to 10 years or more

[MontanoLoza 2021]. In late stage PBC, patients may develop progressive jaundice, portal hypertension, and liver failure, sometime 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]. Through changes in clinical practice (more widely available routine laboratory testing and AMA testing), and enhanced awareness of PBC, many patients are being diagnosed with PBC at an earlier disease stage and over 60% of the newly diagnosed cases are asymptomatic. The majority of asymptomatic patients become symptomatic within 10 years of diagnosis and the estimates for developing symptoms at 5 and 20 years are 50% and 95%, respectively [Prince 2004].

The most common symptoms of PBC are fatigue and pruritus [Crosignani 2008]. Fatigue is reported in up to 80% of patients with PBC [Huet 2000, Cauch-Dudek 1998]. Pruritus, which is usually worse at night, is reported in up to 70% of patients with PBC and its onset generally precedes the onset of jaundice by months to years [Lindor 2019, Al-Harthy 2012]. No correlation between fatigue or pruritus and the severity of the liver disease, histologic stage or duration has been demonstrated [Levy 2023, Hirschfield 2011, Cauch-Dudek 1998]. The mechanisms underlying these symptoms are not well elucidated.

If PBC is left untreated, or if the response to available therapy is incomplete, there is an increased risk of cirrhosis and liver failure, leading to the reduced survival of patients with PBC compared to the general population [EASL 2017, Al-Harthy 2012]. The symptomatic status at diagnosis impacts the prognosis of the patients with PBC. The median survival for symptomatic untreated patients ranges from 5 to 8 years from the onset of symptoms [Springer 1999, Prince 2002]. Symptomatic patients have 10 to 20% higher 10-year cumulative incident rates of developing portal hypertension-related complications compared to asymptomatic individuals at diagnosis. About one quarter of the symptomatic patients at diagnosis progress to liver failure within 10 years. The terminal phase, defined as the serum bilirubin reaching 6 mg/dL with or without gastrointestinal bleeding, ascites, or encephalopathy, is initiated once a patient develops progressive jaundice. This terminal phase can last up to 2 years [Prince 2002].

Histological stages predict the chance of cirrhosis development and therefore predicts the survival [Christensen 1986, Locke 1996, Corpechot_2000]. However, patients with PBC progress at varying rates, with some experiencing liver decompensation over several years while others over decades [AlHarthy 2012, Selmi 2011]. Despite its rarity, PBC remains an important cause of morbidity in the Western world and is one of the leading indications for liver transplantation.

In addition, PBC has been identified as an important risk factor for hepatocellular carcinoma [Ali 2015]. Therefore, routine monitoring for hepatocellular cancer is recommended for patients with PBC [EASL 2017].

Important comorbidities and concomitant medications:

It is estimated that over 80% of patients with PBC will develop a concomitant autoimmune disease at some point, most commonly Sjögren syndrome, thyroid disease, Raynaud's disease, systemic sclerosis, fibrosing alveolitis, and less commonly CREST syndrome (calcinosis, Raynaud's, oesophageal dysfunction, sclerodactyly and telangiectasias), Addison's disease, celiac disease, glomerulonephritis, vitiligo and myasthenia gravis [Floreani 2015, Al-Harthy 2012, Chalifoux 2017]. Hyperlipidaemia is common in patients with PBC [Allocca 2006]. Hypercholesterolemia is common in patients with PBC but is not consistently associated with atherosclerosis [Allocca 2006] nor with an excess risk of cardiovascular disease [Longo 2002]. Concomitant medications for these associated conditions can therefore be used by patients with PBC, including immune modulators and lipid-lowering medications. None of these co-medications are expected to interact with elafibranor. None of these co-medications are expected to increase the risks associated with elafibranor, except statin drugs which may increase the risk of muscle injury/rhabdomyolysis.

For treatment of common symptoms of PBC, such as pruritus, off-label use of cholestyramine, rifampin, naltrexone, and sertraline is attempted to manage symptoms but with varying success. Based on the current knowledge, no drug-drug interaction between these medications and elafibranor is expected.

Part II: Module SII – Nonclinical Part of the Safety Specification

Key findings from in vitro studies:

Both elafibranor and its principal active metabolite GFT1007 are agonists of PPARα, PPARδ and PPARγ in vitro, with approximately a 3- to 8-fold more potent activity on PPARα than on PPARδ and PPARγ. Despite their ability to activate PPARγ in vitro, multiple lines of evidence from safety pharmacology, and repeat-dose toxicology studies with elafibranor clearly show that elafibranor treatment does not induce PPARγ-associated adverse effects (see "Other toxicity-related information or data" section below).

Elafibranor is a multiple but selective kinase inhibitor, as shown by the inhibition of 27 out of 300 kinases tested. Half maximal inhibitory concentration (IC_{50}) values range from 0.87 µM (for platelet-derived growth factor receptor alpha [PDGFRα]) to 24.13 µM (for p21 activated kinase 2 [PAK2]). The corresponding ratio between the IC_{50} and the free human maximum plasma concentration (C_{max}) of elafibranor (from the phase II PBC (GFT505B-216-1, hereafter referred to as Study 2161) clinical study report) was at least >100 for all kinases except for PDGFRα kinase (with a ratio of 66, leading to the conclusion that inhibition of these kinases is unlikely to induce side effects in humans. Additionally, GFT1007 did not show any activity against 15 kinases tested in vitro.

Elafibranor and its main metabolites were also tested against 67 off-target receptors, channels, transporters, and 5 cytochromes P450; none of them inhibited or activated any of the targets, except for GFT1326 metabolite which displayed 62% inhibition of the alpha-2 adrenergic receptor at 10 µM. However, an excretion mass balance study (GFT505-114-10) confirmed that GFT1326 was not identified as a major metabolite in humans.

Key safety findings from nonclinical studies and relevance to human usage:

Toxicity:

- *Key issues identified from acute or repeat-dose toxicity studies:*

The safety of elafibranor was assessed in multiple nonclinical toxicology studies according to the International Council for Harmonisation (ICH) guidelines. Elafibranor exhibited a favourable safety profile when administered as single oral doses in acute toxicity studies in rats and mice. In addition, repeat-dose oral administration for up to 26 weeks in rats and 52 weeks in monkeys did not reveal any sign of human-relevant toxicity up to the maximum tested dose of 100 and 50 mg/kg/day, respectively.

In repeat-dose toxicity studies in rodents, administration of elafibranor to mice up to 30 mg/kg/day for 13 weeks and to rats up to 100 mg/kg/day for 26 weeks induced liver findings, such as liver weight increase and hepatocellular hypertrophy. These findings were generally observed at all dose levels and increased with the dose of elafibranor. However, rodents are known to be susceptible to PPARα-induced hepatomegaly and peroxisomal proliferation [Kobets 2018], of which the relevance to primates including humans is doubtful. Indeed, numerous studies with various fibrates have previously demonstrated that these liver effects observed in rodents are not relevant to humans [Cattley 1998, Pugh 2000, Klaunig 2003, Corton 2018].

Relevance to human usage:

From the findings of repeat-dose toxicity studies, no risks are anticipated in humans.

- *Reproductive/developmental toxicity:*

Two fertility and early embryonic development (FEED) studies were performed in rats, and embryo-foetal development (EFD) studies were performed in pregnant rats and rabbits. Elafibranor was also tested in a pre- and post-natal development (PPND) study in the rat.

In the first FEED rat study, both sexes received elafibranor for either 4 weeks (males) or 2 weeks (females) before pairing for mating. In the second study, only the males received elafibranor, for 4 weeks premating. Both studies used doses up to 100 mg/kg/day and included assessment of sperm parameters. Taking the results from both studies together, there is no adverse effect on rat fertility or early embryonic development at up to 100 mg/kg/day.

Embryo-foetal development study in rats demonstrated that elafibranor was not associated with adverse changes affecting embryo-foetal survival or foetal development at exposures well above the human

exposure. Indeed, none of the pregnancy parameters were affected and no elafibranor treatment-related foetal variation or malformations was noted up to 300 mg/kg/day (~100-fold the human exposure). At the high dose of 1000 mg/kg/day (~165-fold the human exposure), maternal toxicity was evident and was associated with a high post-implantation loss and reduced foetal body weight but there were no elafibranor-related foetal malformations. In an EFD study in pregnant rabbits, maternal toxicity was evident from the mid-dose (100 mg/kg/day). At the highest tested dose (300 mg/kg/day, corresponding to ~3-fold the human exposure), there were increased embryo-lethality, reduced foetal weight plus a low incidence of foetal malformations, predominantly affecting the cardiovascular system, kidney and caudal vertebrae. At 100 mg/kg/day (~0.5-fold the human exposure), none of the pregnancy parameters (including mean foetal body weights) were affected by elafibranor and the only effects on foetal development were delayed and/or incomplete ossification probably resulting from maternal toxicity observed at this dose.

When administered to rats through pregnancy and lactation (PPND study), elafibranor was associated with reduced pup survival (especially in the early perinatal period), lower pup body weights and developmental delays at all dose levels (from 2-fold the clinical exposure). Pale and dilated abdominal blood vessels, blue discolouration of caudal extremities, and/or reduced mobility also occurred in these groups. However, despite these early post-natal effects, adult offspring showed no effects of elafibranor on learning and memory, reflex development, or reproductive capability.

Looking at the overall pattern of developmental effects associated with elafibranor administration to pregnant animals, there are several similarities to the classic PPARα agonist fenofibrate. With the lipid-lowering fenofibrate, there was a particular sensitivity of the developing foetus in late gestation. For example, fenofibrate administration of approximately 7 times the Maximum Recommended Human Dose (MRHD) to female rats only in late gestation from gestation Day 15 through weaning caused a 40% decrease in live births, a 75% decrease in neonatal survival, as well as decreases in pup birth and post-partum weights [Triglide (fenofibrate) USPI]. When fenofibrate was dosed throughout gestation and parturition into lactation at approximately 9-fold the MRHD, there was only 40% survival of pups at birth and a 4% survival of neonates. This is the similar pattern as with elafibranor in the rat where there is a marked difference in the NOAEL/LOAEL in the EFD study versus the PPND study. Other PPARα agonist fibrates such as clofibrate have also been reported to cause perinatal mortality and also reversible hepatomegaly in rat pups [Nyitray 1980]. Gemfibrozil caused dose-related decreases in birthweight and suppression of rat pup growth during lactation [Lopid (gemfibrozil) USPI]. It is considered likely that the adverse effects of elafibranor in the PPND study may be PPARα agonist related. It is also noteworthy that when the PPARα agonists fenofibrate and gemfibrozil were dosed during organogenesis, like elafibranor, rabbits were considered more sensitive than rats regarding the serious developmental toxicity consequences [Tricor (fenofibrate) USPI, Lopid (gemfibrozil) USPI]. For example, gemfibrozil administration at close to clinical doses in rabbits resulted in a dose-related decrease in litter size [Lopid (gemfibrozil) USPI].

Relevance to human usage:

Studies in pregnant animals with elafibranor indicate adverse effects (foetal loss, malformations, stillbirths and/or perinatal deaths) at clinically relevant exposure. Therefore, elafibranor is contraindicated during pregnancy. If a patient becomes pregnant, treatment with elafibranor should be discontinued. Women of childbearing potential have to use effective contraception during and up to at least three weeks following the final dose of elafibranor. Additionally, elafibranor should not be used during breastfeeding and for at least three weeks following last dose of elafibranor.

- *Genotoxicity:*

Elafibranor, its main active metabolite GFT1007, and acyl glucuronide metabolite racemic GFT3351 were all negative in the standard battery of genotoxicity studies.

Relevance to human usage:

The risk of mutagenicity and genotoxicity after oral administration of elafibranor in humans is considered minimal.

- *Carcinogenicity:*

The 2-year repeat-dose carcinogenicity studies in mice and rats were completed. The only consistent safety concern raised by these studies is the expected PPARα-associated hepatomegaly, hepatocellular hypertrophy and liver carcinoma in rodent species (mice and rats). However, it is well known that, compared to nonhuman primates and humans, rodents are highly sensitive to PPARα agonist-induced peroxisome proliferation and associated liver side effects. Thus, available information on marketed PPARα agonists, together with the lack of any liver side effects in monkeys treated with high doses of elafibranor for 1 year, supports the nonrelevance to humans [Cattley 1998, Corton 2018].

Relevance to human usage:

The risk of carcinogenicity after oral administration of elafibranor in humans is considered minimal.

Safety pharmacology:

No safety issues were identified when assessing the potential effects of elafibranor on the cardiovascular, respiratory and central nervous systems in nonclinical species.

Other toxicity-related information or data:

- *PPARγ agonism:*

It is to be noted that up to the highest doses tested, elafibranor did not show any relevant effects on organs and systems previously described as being of a safety concern with PPARγ agonists (weight gain, haemodilution, fluid retention leading to congestive heart failure and bladder cancer) [Wright 2014]. Indeed, safety pharmacology studies in mice and rats as well as toxicology studies in multiple species showed that repeat-dose administration of elafibranor did not induce weight gain and had little or no effect on red blood cell parameters including haematocrit. Additionally, in the 6-month toxicology study in rats, elafibranor treatment did not increase plasma levels of adiponectin, a marker of PPARγ activation [Amin 2010]. Finally, the 2-year carcinogenicity studies in mice and rats revealed no PPARγ-associated tumours, and notably no increase in bladder carcinoma.

Relevance to human usage:

Based on these findings, no PPARγ agonism is anticipated.

- *Phototoxicity:*

Elafibranor, but not its major metabolite d1007, showed UVA-dependent cytotoxicity in the vitro assay 3T3 fibroblasts. In the follow-up UV-LLNA mice study the highest tested dose of 800 mg/kg/day elafibranor there were isolated findings in one animal out of six. The severity and occurrence of the findings were low, and no increase in the lymph node cell count was noted in any animal. At the dose of 800 mg/kg/day, the exposure margin compared to the human therapeutic dose of 80 mg/day is high (i.e. 46-fold) based on unbound C_{max} for elafibranor. It is therefore concluded that there is no in vivo phototoxic risk associated with elafibranor. Moreover, tissue distribution studies using radiolabelled elafibranor in mice, rats and monkeys showed that there was no accumulation of elafibranor in eyes and skin, which limits its phototoxic potential.

Relevance to human usage:

Based on these findings, no phototoxicity is anticipated.

- *Juvenile toxicity:*

A juvenile toxicity study was performed in rats, with the administration of elafibranor from the post-natal day (PND) 21 to PND 63 (6 weeks), in order to cover the periods of childhood and adolescence (age 2 to less than 18 years). An assessment of delayed onset toxicity and/or reversibility of toxicity was made following a 4-week recovery period. Overall, changes observed during the study were either minor and manageable (and at least partially reversible) or recognised as adaptive changes associated with the PPARα agonists in rats. Therefore, the NOAEL for male and female juvenile rats was considered to be the highest tested dose (100 mg/kg/day) of elafibranor.

- *Safety margins:*

The exposure margins derived from the package of nonclinical safety studies conducted as per appropriate guidance are presented in the Table 3 below. As elafibranor and its active metabolite

GFT1007 show a comparable potency on the PPAR subtypes in rodents and humans, safety margins were calculated based on total active exposure (elafibranor plus GFT1007). Unbound exposures were calculated based on the unbound fractions determined for each species and compared to steady state unbound plasma exposures observed at 80 mg/day in participants with PBC. The combined results from the nonclinical package support the use of elafibranor at 80 mg/day for the treatment of patients with PBC, including women of childbearing potential.

Table 3 Safety Margins Calculated by NOAEL Compared to Participants with PBC Treated with Elafibranor

Study	**Elafibranor dose**	**AUC0-24 unbound [a] GFT505 (ng*h/mL)**	**AUC0-24 unbound GFT1007 (ng*h/mL)**	**AUC0-24 unbound GFT505+ GFT1007 (ng*h/mL)**	**Exposure margin at 80 mg/day**
Human, Participants with PBC [b] (GFT505B-216-1)	80 mg/day	23.7	45.5	69.2	N/A
12-month monkey study (GFT505-TOX3-009)	50 mg/kg/day (NOAEL)	82.6	1002	1085	15.7
6-month rat study (GFT505-TOX3-008)	100 mg/kg/day (NOAEL with the exception of the liver)	345	717	1063	15.4
PK study in gestating rats (GFT505-KIN3-033)	300 mg/kg/day (NOEL for developmental toxicity in EFD study GFT505-TOX5_002)	635	6274	6909	99.8
PK study in gestating rabbits (IPS001016)	30 mg/kg/day (NOAEL for developmental toxicity in EFD study GFT505-TOX5_004)	0.3	7.1	7.3	0.1
PPND rat study (GFT505-TOX5-006)	10 mg/kg/day (LOAEL)	8.1	135.3	143.4	2.1
Study	**Elafibranor dose**	**C_{max} unbound GFT505 (ng/mL)**		**Exposure margin at 80 mg/day**	
Human, PBC participants [b]	80 mg/day	5.05		NA	
UV-LLNA phototoxicity study in Balb/c mice (GFT505-TOX6-003)	800 mg/kg/day (NOAEL)	231.4		45.8	

AUC_{0-24} under the plasma concentration-time curve from time zero up to 24 hours after administration (since the molecular weights of GFT505 and GFT1007 are only marginally different, exposure margins were calculated based on plasma concentrations in ng/mL rather than molar concentrations); C_{max}=maximum concentration of drug after administration; EFD=embryo-foetal development; LOAEL=Low Observed Adverse Effect Level; NA=not applicable; NOAEL=No-Observed Adverse Effect Level; NOEL=No-Observed Effect Level; PK=pharmacokinetics; PBC=primary biliary cholangitis; UV-LLNA= Ultraviolet Local Lymph Node Assay.

a Unbound plasma exposures were calculated based on the following values for unbound fraction determined in Study GFT505KIN1007c and Study IPS001012 - IPS/27. Elafibranor: Mouse 0.0243; Rat 0.0179; Rabbit: 0.005; Monkey 0.0163; Human 0.0063; GFT1007: Rat 0.0145; Rabbit: 0.0035; Monkey 0.0224; Human 0.0038.

b Pharmacokinetic (PK) data from phase II PBC Study 2161 after 2 weeks of daily elafibranor administration.

AUC.

Part II: Module SIII – Clinical Trial Exposure

Up to 01 June 2023 (Data cut-off of the CSR [DBP] for the phase III PBC Study GFT505B-319-1, [hereafter referred to as Study 319-1]), the total number of participants enrolled in the elafibranor clinical programme by completed studies and completed DBP of ongoing Study 319-1 is 3745, of whom 2588 were exposed to elafibranor.

Study 319-1 is a 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 DBP (the first 52 weeks of treatment period) and up to a maximum of 104 weeks (the overall DBP). At the time of data cut-off for the Study 319-1 DBP CSR (01 June 2023), the last participant had completed the Week 52 visit for Study 319-1. A total of 161 enrolled participants have been exposed to at least one administration of blinded study medication/placebo with 108 participants exposed to elafibranor in this study.

In the phase I programme, the administered elafibranor daily doses ranged between 5 mg and 360 mg, with a treatment duration of up to 16 days. In the phase II programme conducted in different indications, including Fredrickson type 2b dyslipidaemia (mixed hyperlipidaemia), atherogenic dyslipidaemia, diabetes/prediabetes, impaired glucose tolerance, nonalcoholic fatty liver, NASH and PBC, the administered elafibranor daily doses ranged between 30 mg and 120 mg, with a maximum treatment duration of 52 weeks. Dosing regimens in the phase III studies were either 80 mg or 120 mg daily, with exposure up to 221 weeks for 120 mg (NASH phase III Study 315-1) and a projected exposure up to 6 years for 80 mg (phase III PBC Study 319-1). Table 4 summarises overall exposure across all indications, in all studies completed with elafibranor and in the completed DBP of ongoing Study 319-1.

Table 5a and Table 5b provides the cumulative participant exposure to elafibranor from clinical studies by duration of exposure in the PBC and NASH clinical indications, respectively. Table 6a and

Table 6b provides the cumulative participant exposure to elafibranor from clinical studies by dose in the PBC and NASH clinical indications, respectively.

Table 7a and Table 7b provides the cumulative participant exposure to elafibranor from clinical studies by age group and gender in the PBC and NASH clinical indications, respectively. Table 8a and Table 8b provides the cumulative participant exposure to elafibranor from clinical studies by race in the PBC and NASH clinical indications, respectively. Table 9a and Table 9b provides the cumulative participant exposure to elafibranor from clinical studies by ethnic origin in the PBC and NASH clinical indications, respectively.

Table 4 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
		GFT505B-319-1 [a]	III	108 [f]	53 [f]	161
		GFT505b 216-1	II	30	15	45
Other Indications	Hepatic Indications					
	NASH	Total		1,625	809	2,434
		GFT505-315-1 [b]	III	1,433 [f]	717	2,150
		GFT505-212-7	IIb	182	92	274
		GFT505e-218-1 [c]	IIa	10	-	10
	NAFLD	GFT505-219-8	II	13	13	17 [d]
	Non-hepatic Indications					
	Diabetes Mellitus	Total		59	50	109

Study Details				Number of Participants Treated		
Study Indication		**Study ID**	**Phase**	**Elafibranor**	**Placebo**	**Total**
		GFT505-210-5	IIa	50	47	97
		GFT505-111-7 (Part 4)	I	9	3	12
	Obesity/Overweight and/or abnormal glucose tolerance	Total		90	61	129
		GFT505-209-4	IIa	23	24	47
		GFT505-210-6	IIa	22	22	22 [e]
		GFT505-111-7 (Part 2)	I	18	6	24
		GFT505-111-7 (Part 3)	I	27	9	36
	Dyslipidaemia/ Hyperlipidaemia	Total		87	44	131
		GFT505-208-3	IIa	63	31	94
		GFT505-207-1	IIa	24	13	37
Special population/ Healthy participants	Renal impairment	GFT505-118-13	I	13	0	13
	Hepatic impairment	GFT505-118-14	I	20 [f]	0	20
	Healthy participants	Phase I studies [g]	I	543	143	686
	Elderly participants [f] (≥75 years)	GFT505-119-16	I	11 [f]	0	11
	QTc interval study	GFT505-113-9 Part 2	I	89	87	176
Total number of participants exposed				2,588	1,188	3,745

CSR=clinical study report; DBP=double-blind period; LTE=long-term extension; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis; PBC=primary biliary cholangitis; QTc=corrected QT.

a The DBP of the phase III PBC Study 319-1 has been completed, whereas the LTE is currently ongoing.

b Safety population includes all participants who received one 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.

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 Of note, exposure data have also been included for Study CLIN-60190-452 (conducted in healthy participants) as the CSR for this study was issued on 08 June 2023.

Table 5a Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Primary Biliary Cholangitis Indication by Duration of Exposure

		Duration of exposure				
Study	**Parameter [a]**	**<4 weeks**	**4 to <12 weeks**	**12 to ≤52 weeks**	**>52 weeks**	**Total**
Phase III Study 319-1 [b]	Number of patients	1	1	31	75	108
	Person-time (person-weeks)	1.1	9.6	1408.0	5730.3	7149.0
	Person-time (person-years)	0.0	0.2	27.0	109.8	137.0
Phase II Study 216-1 [c]	Number of patients	1	4	25	0	30
	Person-time (person-weeks)	0.3	47.0	308.4	0.0	355.7
	Person-time (person-years)	0.0	0.9	5.9	0.0	6.8
Total	Number of patients	2	5	56	75	138
	Person-time (person-weeks)	1.4	56.6	1716.4	5730.3	7504.7
	Person-time (person-years)	0.0	1.1	32.9	109.8	143.8

a Person-weeks are calculated as exposure duration (in days)/7. Person-years are calculated as exposure duration (in days)/365.25.
b 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 patient 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.
c For Study 216-1, exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1.

Table 5b Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Nonalcoholic Steatohepatitis Indication by Duration of Exposure

Study	Parameter [a]	Duration of exposure				
		<4 weeks	4 to <12 weeks	12 to ≤52 weeks	>52 weeks	Total
Phase III Study 315-1 [b]	Number of patients	14	14	197	1208	1433
	Person-time (person-weeks)	13.7	109.4	6620.9	142091.6	148835.6
	Person-time (person-years)	0.3	2.1	126.9	2723.2	2852.4
Phase IIb Study 212-7	Number of patients	1	5	109	67	182
	Person-time (person-weeks)	0.6	45.3	5323.0	3526.0	8894.9
	Person-time (person-years)	0.0	0.9	102.0	67.6	170.5
Phase IIa Study 218-1	Number of patients	0	3	7	0	10
	Person-time (person-weeks)	0.0	35.1	85.3	0.0	120.4
	Person-time (person-years)	0.0	0.7	1.6	0.0	2.3
Total	Number of patients	15	22	313	1275	1625
	Person-time (person-weeks)	14.3	189.9	12029.1	145617.6	157850.9
	Person-time (person-years)	0.3	3.6	230.5	2790.8	3025.2

a For all studies exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1. Person-weeks are calculated as exposure duration (in days)/7. Person-years are calculated as exposure duration (in days)/365.25.
b For Study 315-1, exposure duration is from the long-term endpoint analysis using the full safety set.

Table 6a Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Primary Biliary Cholangitis Indication by Dose

Study	Parameter [a]	Dose		
		80 mg/day	120 mg/day	Total
Phase III Study 319-1 [b]	Number of patients	108	NA	108
	Person-time (person-weeks)	7149.0	NA	7149.0
	Person-time (person-years)	137.0	NA	137.0
Phase II Study 216-1 [c]	Number of patients	15	15	30
	Person-time (person-weeks)	184.7	171.0	355.7
	Person-time (person-years)	3.5	3.3	6.8
Total	Number of patients	123	15	138
	Person-time (person-weeks)	7333.7	171.0	7504.7
	Person-time (person-years)	140.6	3.3	143.8

NA=Not applicable.
a Person-weeks are calculated as exposure duration (in days)/7. Person-years are calculated as exposure duration (in days)/365.25.
b 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 patient 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.
c For Study 216-1, exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1.

Table 6b Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Nonalcoholic Steatohepatitis Indication by Dose

Study	Parameter [a]	Dose		
		80 mg/day	120 mg/day	Total
Phase III Study 315-1 [b]	Number of patients	NA	1433	1433
	Person-time (person-weeks)	NA	148835.6	148835.6
	Person-time (person-years)	NA	2852.4	2852.4
Phase IIb Study 212-7	Number of patients	93	89	182
	Person-time (person-weeks)	4611.6	4283.3	8894.9
	Person-time (person-years)	88.4	82.1	170.5
Phase IIa Study 218-1	Number of patients	5	5	10
	Person-time (person-weeks)	60.6	59.9	120.4
	Person-time (person-years)	1.2	1.1	2.3
Total	Number of patients	98	1527	1625
	Person-time (person-weeks)	4672.1	153178.7	157850.9
	Person-time (person-years)	89.5	2935.7	3025.2

a For all studies, exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1. Person-weeks are calculated as exposure duration (in days)/7. Person-years are calculated as exposure duration (in days)/365.25.

b For Study 315-1, exposure duration is from the long-term endpoint analysis using the full safety set. For all studies exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1.

Table 7a Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Primary Biliary Cholangitis Indication by Age Group and Gender

Study	Parameter [a]	Gender	Age Group (years)				
			18 – 64	65 – 74	75 – 84	≥85	Total
Phase III Study 319-1 [b]	Number of patients	Male	5	1	0	0	6
		Female	78	23	1	0	102
		Total	83	24	1	0	108
	Person-time (person-weeks)	Male	344.4	51.6	0.0	0.0	396.0
		Female	5278.3	1422.9	51.9	0.0	6753.0
		Total	5622.7	1474.4	51.9	0.0	7149.0
	Person-time (person-years)	Male	6.6	1.0	0.0	0.0	7.6
		Female	101.2	27.3	1.0	0.0	129.4
		Total	107.8	28.3	1.0	0.0	137.0
Phase II Study 216-1 [c]	Number of patients	Male	1	0	0	0	1
		Female	22	7	0	0	29
		Total	23	7	0	0	30
	Person-time (person-weeks)	Male	12.1	0.0	0.0	0.0	12.1
		Female	269.9	73.7	0.0	0.0	343.6
		Total	282.0	73.7	0.0	0.0	355.7
	Person-time (person-years)	Male	0.2	0.0	0.0	0.0	0.2
		Female	5.2	1.4	0.0	0.0	6.6
		Total	5.4	1.4	0.0	0.0	6.8
Total	Number of patients	Male	6	1	0	0	7
		Female	100	30	1	0	131

		Total	106	31	1	0	138
	Person-time (person-weeks)	Male	356.6	51.6	0.0	0.0	408.1
		Female	5548.1	1496.6	51.9	0.0	7096.6
		Total	5904.7	1548.1	51.9	0.0	7504.7
	Person-time (person-years)	Male	6.8	1.0	0.0	0.0	7.8
		Female	106.3	28.7	1.0	0.0	136.0
		Total	113.2	29.7	1.0	0.0	143.8

[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 patient 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 patient is calculated as the last dose date – first dose date + 1.

For 216-1 80 mg: For Patient 8260601 the date of Visit 5 was incorrectly recorded. This patient was removed from the Clinical Study Report analysis of patients with reliable exposure data.

For 216-1 120 mg: Patient 8400201 withdrew from the study one day after their first study drug intake. In the Clinical Study Report this patient is not considered in the descriptive statistics due to a missing date for the patient's last study drug intake. However, for the RMP tables the maximum of EX.EXSTDTC/EX.EXENDTC has been used as last dose date and this was one day after the first dose date.

Person-weeks are calculated as exposure duration (in days)/7.

Person-years are calculated as exposure duration (in days)/365.25.

Table 7b Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Nonalcoholic Steatohepatitis Indication by Age Group and Gender

Study	Parameter [a]	Gender	Age Group (years)					
			<18	18 – 64	65 – 74	75 – 84	≥85	Total
Phase III Study 315-1 [b]	Number of patients	Male	0	663	144	5	0	812
		Female	0	480	139	2	0	621
		Total	0	1143	283	7	0	1433
	Person-time (person-weeks)	Male	0.0	66422.7	14211.3	577.0	0.0	81211.0
		Female	0.0	51709.4	15668.4	246.7	0.0	67624.6
		Total	0.0	118132.1	29879.7	823.7	0.0	148835.6
	Person-time (person-years)	Male	0.0	1273.0	272.4	11.1	0.0	1556.4
		Female	0.0	991.0	300.3	4.7	0.0	1296.0
		Total	0.0	2264.0	572.6	15.8	0.0	2852.4
Phase Iib Study 212-7	Number of patients	Male	0	86	10	0	0	96
		Female	0	73	11	2	0	86
		Total	0	159	21	2	0	182
	Person-time (person-weeks)	Male	0.0	4084.0	521.4	0.0	0.0	4605.4
		Female	0.0	3612.9	573.4	103.1	0.0	4289.4
		Total	0.0	7696.9	1094.9	103.1	0.0	8894.9
	Person-time (person-years)	Male	0.0	78.3	10.0	0.0	0.0	88.3
		Female	0.0	69.2	11.0	2.0	0.0	82.2
		Total	0.0	147.5	21.0	2.0	0.0	170.5
Phase Iia Study 218-1	Number of patients	Male	10	0	0	0	0	10
		Female	0	0	0	0	0	0
		Total	10	0	0	0	0	10
	Person-time (person-weeks)	Male	120.4	0.0	0.0	0.0	0.0	120.4

		Female	0.0	0.0	0.0	0.0	0.0	0.0
		Total	120.4	0.0	0.0	0.0	0.0	120.4
	Person-time (person-years)	Male	2.3	0.0	0.0	0.0	0.0	2.3
		Female	0.0	0.0	0.0	0.0	0.0	0.0
		Total	2.3	0.0	0.0	0.0	0.0	2.3
Total	Number of patients	Male	10	749	154	5	0	918
		Female	0	553	150	4	0	707
		Total	10	1302	304	9	0	1625
	Person-time (person-weeks)	Male	120.4	70506.7	14732.7	577.0	0.0	85936.9
		Female	0.0	55322.3	16241.9	349.9	0.0	71914.0
		Total	120.4	125829.0	30974.6	926.9	0.0	157850.9
	Person-time (person-years)	Male	2.3	1351.3	282.4	11.1	0.0	1647.0
		Female	0.0	1060.2	311.3	6.7	0.0	1378.2
		Total	2.3	2411.5	593.6	17.8	0.0	3025.2

[a]For Study 315-1, exposure duration is from the long-term endpoint analysis using the full safety set.

For all studies exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1.

Person-weeks are calculated as exposure duration (in days)/7.

Person-years are calculated as exposure duration (in days)/365.25.

Table 8a Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Primary Biliary Cholangitis Indication by Race

Study	Parameter [a]	Race					
		White	Black or African American	Asian	Other [b]	Missing [c]	Total
Phase III Study 319-1 [d]	Number of patients	101	2	1	3	1	108
	Person-time (person-weeks)	6735.1	117.3	56.0	190.1	50.4	7149.0
	Person-time (person-years)	129.1	2.2	1.1	3.6	1.0	137.0
Phase II Study 216-1 [e]	Number of patients	30	0	0	0	0	30
	Person-time (person-weeks)	355.7	0.0	0.0	0.0	0.0	355.7
	Person-time (person-years)	6.8	0.0	0.0	0.0	0.0	6.8
Total	Number of patients	131	2	1	3	1	138
	Person-time (person-weeks)	7090.9	117.3	56.0	190.1	50.4	7504.7
	Person-time (person-years)	135.9	2.2	1.1	3.6	1.0	143.8

a Person-weeks are calculated as exposure duration (in days)/7. Person-years are calculated as exposure duration (in days)/365.25.
b 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander'.
c 'Not reported', 'Unknown', and missing values.
d 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 patient 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.
e For Study 216-1, exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1.

Table 8b Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Non-Alcoholic Steatohepatitis Indication by Race

Study	Parameter [a]	Race					
		White	Black or African American	Asian	Other [b]	Missing [c]	Total
Phase III Study 315-1 [d]	Number of patients	1230	28	53	104	18	1433
	Person-time (person-weeks)	127572.3	2439.0	5882.7	11263.6	1678.0	148835.6
	Person-time (person-years)	2444.9	46.7	112.7	215.9	32.2	2852.4
Phase IIb Study 212-7	Number of patients	159	7	6	10	0	182
	Person-time (person-weeks)	7756.9	331.7	311.9	494.4	0.0	8894.9
	Person-time (person-years)	148.7	6.4	6.0	9.5	0.0	170.5
Phase IIa Study 218-1	Number of patients	5	0	0	5	0	10
	Person-time (person-weeks)	59.7	0.0	0.0	60.7	0.0	120.4
	Person-time (person-years)	1.1	0.0	0.0	1.2	0.0	2.3
Total	Number of patients	1394	35	59	119	18	1625
	Person-time (person-weeks)	135388.9	2770.7	6194.6	11818.7	1678.0	157850.9
	Person-time (person-years)	2594.7	53.1	118.7	226.5	32.2	3025.2

a Person-weeks are calculated as exposure duration (in days)/7. Person-years are calculated as exposure duration (in days)/365.25.
b 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander'.
c 'Not reported', 'Unknown', and missing values.
d For Study 315-1, exposure duration is from the long-term endpoint analysis using the full safety set. For all studies exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1.

Table 9a Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Primary Biliary Cholangitis Indication by Ethnicity

Study	Parameter [a]	Ethnicity		
		Hispanic or Latino	Not Hispanic or Latino	Total
Phase III Study 319-1 [b]	Number of patients	NC	NC	NC
	Person-time (person-weeks)	NC	NC	NC
	Person-time (person-years)	NC	NC	NC
Phase II Study 216-1 [c]	Number of patients	5	25	30
	Person-time (person-weeks)	63.4	292.3	355.7
	Person-time (person-years)	1.2	5.6	6.8

NC=Not collected.
a Person-weeks are calculated as exposure duration (in days)/7. Person-years are calculated as exposure duration (in days)/365.25.
b For Study 319-1, ethnicity was not collected.
c For Study 216-1, exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1.

Table 9b Cumulative Participant Exposure to Elafibranor from Clinical Trials in the Non-Alcoholic Steatohepatitis Indication by Ethnicity

Study	Parameter [a]	Ethnicity			
		Hispanic or Latino	Not Hispanic or Latino	Missing [b]	Total
Phase III Study 315-1 [c]	Number of patients	335	1087	11	1433
	Person-time (person-weeks)	34360.6	113320.7	1154.3	148835.6
	Person-time (person-years)	658.5	2171.8	22.1	2852.4
Phase IIb Study 212-7	Number of patients	NC	NC	NC	NC
	Person-time (person-weeks)	NC	NC	NC	NC
	Person-time (person-years)	NC	NC	NC	NC
Phase IIa Study 218-1	Number of patients	9	1	0	10
	Person-time (person-weeks)	108.1	12.3	0.0	120.4
	Person-time (person-years)	2.1	0.2	0.0	2.3
Total	Number of patients	344	1088	11	1443
	Person-time (person-weeks)	34468.7	113333.0	1154.3	148956.0
	Person-time (person-years)	660.6	2172.0	22.1	2854.7

NC=Not collected.
a For all studies exposure duration (in days) for each patient is calculated as the last dose date – first dose date + 1. Person-weeks are calculated as exposure duration (in days)/7. Person-years are calculated as exposure duration (in days)/365.25.
b 'Not reported', 'Unknown', and missing values.
c For Study 315-1, exposure duration is from the long-term endpoint analysis using the full safety set.

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 10 provides an overview of the important exclusion criteria in the pivotal clinical phase III PBC Study 319-1 and whether they are considered missing information and the rationale.

Table 10 Important Exclusion Criteria in the Primary Biliary Cholangitis Pivotal Clinical Study (GFT505B-319-1)

Exclusion criteria	Reason for exclusion	Missing information (Yes/no)	Rationale (if not considered missing information)
Younger than 18 years old	Product-specific paediatric waiver has been granted by EMA.	No	PBC does not generally occur in the paediatric population.
Older than 75 years old	To optimise the benefit-risk balance for the patients and to not confound clinical study data due to age-related comorbidities.	No	There is no significant difference expected in the behaviour of the disease or the effect of elafibranor -related to older age. Age was investigated as part of the covariate analysis in the population PK (PopPK) analysis (REP-PK2-IPS-ELA-PMX-1) across a range of ages in participants who were 18 to 80 years old. No clinically relevant effect of age could be seen on AUC across dosing interval, C_{max} or trough concentration of elafibranor or GFT1007 at steady state for participants with PBC.
Female patients with known pregnancy or who have a positive serum pregnancy test, or lactating	Nonclinical data indicated potential teratogenicity/ foetotoxicity risk.	No	Elafibranor is contraindicated during known or suspected pregnancy.
Patients with clinically significant hepatic decompensation, including participants with: History of liver transplantation, current placement on a liver transplant list or current MELD-Na score ≥12 linked to hepatic impairment Cirrhosis/portal hypertension complications including known oesophageal varices, ascites, history of variceal bleeds or related interventions (e.g. insertion of variceal bands or TIPS, presence of hepatic encephalopathy, history or presence of spontaneous bacterial peritonitis) Hepatorenal syndrome (type I or II)	The ethics of potential placebo exposure and uncertainty if any intervention improves the condition when a patient reaches this stage limit the inclusion.	No	Elafibranor is not recommended for patients with severe hepatic impairment (Child-Pugh C).
Patients with significant renal disease including nephritic syndrome and chronic kidney disease (defined as participants with markers of kidney failure damage or eGFR <60 mL/min/1.73 m^2 calculated by the MDRD)	A reversible increase in creatinine levels has been observed in a small percentage of participants treated with elafibranor without corresponding symptoms of renal injury; to eliminate any confounding factors in the assessment of renal function, patients with clinically significant decreased eGFR (leading to elevated creatinine), or known significant baseline renal disease, were excluded.	No	The safety of elafibranor in this special population is not expected to differ from the known safety profile. In the PK study GFT505-118-13, severe renal impairment was determined to have no clinically relevant impact on the total plasma exposure of elafibranor and GFT1007. Unbound fractions were low and relatively similar in both healthy participants and ESRD participants.

AUC=area under the curve; C_{max}=maximum concentration; eGFR= estimated glomerular filtration rate; EMA=European Medicines Agency; ESRD=end-stage renal disease; MDRD= modification of diet in renal disease; MELD-Na=Model for End-stage Liver Disease-Sodium; PBC= primary biliary cholangitis; PK=pharmacokinetics; TIPS= transjugular intrahepatic portosystemic shunt.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme to date is unlikely to detect certain types of adverse reactions in the PBC population such as rare adverse events, adverse reactions with a long latency or those caused by prolonged exposure (greater than 2 years). Participants with longer exposure time are to be studied in the ongoing LTE of the phase III PBC Study 319-1 and the ongoing phase III confirmatory Study CLIN-60190-454 (Study 454).

To date, no paediatric participants ≤11 years old have been included in clinical studies of elafibranor. One study in the clinical programme enrolled 10 male participants ages 12 to 17 years in the NASH indication for initial pharmacokinetics (PK) characterisation. No new safety concerns were identified in this study for this population after 29 days of repeated once daily oral dose administration of 80 or 120 mg of elafibranor.

Pregnant and breastfeeding women have been excluded from clinical studies of elafibranor by the requirement of a negative pregnancy test at screening for women of childbearing potential and regular pregnancy testing during treatment. However, 17 cases (including mother, father and child cases) have been reported in the completed clinical studies relating to 11 total pregnancies: 4 pregnancies in elafibranor-treated female participants and 7 pregnancies in female partners of elafibranor-treated male participants. There was no pregnancy or pregnancy-related event reported in the PBC studies.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

The population enrolled in the clinical study development programme has been representative of the planned target population. Table 11 outlines the special populations that have or have not been included in the clinical study development programme with corresponding exposure to elafibranor.

Table 11 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme, but there have been 4 pregnancies reported in female participants exposed to elafibranor (among which one pregnancy started 6 months after elafibranor discontinuation).
Breastfeeding women	Not included in the clinical development programme. No exposure to elafibranor in this special population has been reported to date.
Participants with relevant comorbidities: Autoimmune conditions Hyperlipidaemia	No exclusion of known comorbidities identified for the indication was made unless they were unstable in the participant, except for patients with 'autoimmune hepatitis overlap', who were excluded per protocol. Autoimmune conditions are reported to occur in 84% of the PBC population with the most frequently reported being Sjögren syndrome (70%) and Raynaud's syndrome (20%) [Al-Harthy 2012]. In the phase III PBC Study 319-1, concomitant medical histories included Sjögren's syndrome (16 participants, 9.9%), Raynaud's phenomenon (8 participants, 5.0%), and autoimmune thyroiditis (5 participants, 3.1%). In the phase II PBC Study 216-1, Sjögren syndrome was reported as concomitant medical history in 4.4% (2 participants) and Raynaud's phenomenon was reported in 6.7% of the participants (3 participants). Hyperlipidaemia has been seen in up to 80% of patients with PBC [EASL 2017]. Study 319-1 had an overall 15.5% of participants (25 participants) and Study 216-1 had an overall 17.8% of participants (8 participants) with hyperlipidaemia reported as concomitant medical history.

Type of special population	Exposure
Participants with moderate or severe hepatic impairment	No participants with severe hepatic impairment have been included in the development plan for PBC, NASH, primary sclerosing cholangitis (PSC), diabetes or obesity. A PK study (GFT505-118-14) was conducted in 20 non-PBC participants with hepatic impairment (mild (n=7), moderate (n=7) and severe (n=6)) who received a single dose of 120 mg of elafibranor. Clinical studies in PBC have been restricted to participants with MELD-Na score <12, and to participants with no evidence of clinically significant hepatic decompensation. Therefore, the number of participants with moderate hepatic impairment was low.
Participants with moderate or severe renal impairment	Participants with a significant renal disease have been excluded from the development programme in PBC, NASH, PSC, diabetes and obesity, including participants with severe or moderate renal impairment. A PK study (GFT505-118-13) has been conducted in 13 non-PBC participants with ESRD not yet on dialysis (with eGFR <15 mL/min/1.73m²) who received a single dose of 120 mg of elafibranor. In the clinical studies of participants with PBC, those with chronic kidney disease (eGFR <60 mL/min/1.73 m^2) were excluded.
Population with relevant different ethnic origin	In all studies completed, no race or ethnicity restriction was in place. Relevant racial and ethnic groups for PBC, including Hispanic or Latino, Asian, American Indian/Alaska Native, Black or African American, White, Native Hawaiian or other Pacific Islander, were included in completed and ongoing studies (refer to Table 7 for completed studies).
Subpopulations carrying relevant genetic polymorphisms	Not applicable since no metabolic pathway with relevant polymorphisms has been identified so far.

eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; MELD-Na= Model for End-stage Liver Disease-Sodium; NASH=nonalcoholic steatohepatitis; PBC=primary biliary cholangitis; PSC=primary sclerosing cholangitis; PK=pharmacokinetic.

Part II: Module SV – Post-authorisation Experience

Not applicable as elafibranor is not an authorised product.

SV.1 Post-authorisation Exposure

Not applicable.

SV 1.1 Method used to calculate exposure

Not applicable.

SV 1.2 Exposure

Not applicable.

Part II: Module SVI – Additional EU Requirements for the Safety Specifications

Potential for Misuse for Illegal Purposes

There is no potential of misuse for illegal purposes for elafibranor identified at present.

Part II: Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Table 12 Summary of Safety Concerns from the First Approved RMP

Important identified risks	None
Important potential risks	• Hepatic events • Myopathy including rhabdomyolysis
Missing information	• Long term safety

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that do not impact the risk-benefit profile:

Increased blood creatinine

In the phase II PBC Study 216-1, mean changes in serum creatinine from baseline to end of treatment were +1.4 µmol/L in elafibranor 80 mg arm, +7.6 µmol/L in elafibranor 120 mg arm, and –0.5 µmol/L in placebo arm. Overall, increases in blood creatinine in elafibranor clinical studies were uncommon and returned to normal either without stopping elafibranor (transitory events) or upon elafibranor discontinuation (reversible events). Elevations in serum creatinine were not associated with elevations of other renal markers, such as cystatin C or microalbuminuria, which remained within normal limits, nor with a decrease in eGFR. Despite the exact mechanisms being unknown, the increase in serum creatinine is thought to be due to an increase in the metabolic production rate of creatinine rather than reflecting an impairment of the renal function [Hottelart-2002]. Therefore, in the context of risk management, increased blood creatinine is not considered a safety concern, as there is no clinical outcome associated with this finding, and therefore there is no impact on the benefit-risk balance.

Other reasons for considering the risk not important:

Foetotoxicity and/or teratogenicity

Based on nonclinical data and limited clinical data in the NASH population, elafibranor may adversely impact pregnancy and potentially post-natal development upon maternal exposure. As per Sections 4.3 and 4.6 of EU Summary of Product Characteristics (SmPC), elafibranor is contraindicated during known or suspected pregnancy. If a patient becomes pregnant, treatment with elafibranor should be discontinued. Women of childbearing potential have to use effective contraception during and up to at least three weeks following the final dose of elafibranor. The pregnancy status of patients of childbearing potential should be checked prior to initiation of elafibranor treatment. With this contraindication in place and given the context of rare disease and main target population being at their end of childbearing potential (PBC typically diagnosed in patients between 40 and 60 years of age), there is no reasonable expectation that any pharmacovigilance activity can further characterise the risk. Moreover, there is no reasonable expectation that any current or planned additional pharmacovigilance activities would be able to characterise this safety concern due to the demography of PBC patients, contraindication in place and confounding maternal age-associated risks of congenital anomalies increase.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The risks included in the safety concerns as important identified risks, important potential risks or missing information are discussed below.

Important Identified Risks

There are no identified risks considered important for inclusion as safety concerns for this RMP at present.

Important Potential Risks

The potential risks considered important for inclusion as safety concerns in this RMP are presented in Table 13.

Table 13 Important Potential Risks

Important potential risk	Risk-benefit impact
Hepatic events	Hepatic events are considered as an important potential risk based on one possible DILI (adjudicated by the CEC) reported in a participant receiving elafibranor in the phase III PBC Study 319-1, which could have been related to disease progression. Overall, no imbalance was noted in the occurrence of suspected DILI between participants treated with elafibranor (4/108 [3.7%]) and participants treated with placebo (2/53 [3.8%]) in this study. Given the limited data and the potential impact on the benefit-risk balance, the risk of hepatic events is considered as important potential risk.
Myopathy including rhabdomyolysis	Myopathy including rhabdomyolysis is considered as an important potential risk based on: • One serious TEAE of rhabdomyolysis reported in a participant receiving elafibranor in the phase III PBC Study 319-1, in a context of concomitant treatment with atorvastatin for which rhabdomyolysis is a known adverse drug reaction (same participant as for the above possible DILI) with elafibranor. • Increases in CPK and myalgia have been reported as TEAEs in participants receiving elafibranor in phase III PBC Study 319-1 (blood CPK increased: 3.7% in elafibranor group compared to 0% in placebo group; myalgia: 2.8% in elafibranor group compared to 0% in placebo group). Increases in CPK and myalgia are reported with marketed PPARα agonists. • Blood CPK increased and myalgia are considered as ADRs as per EU SmPC. Given the limited data and the potential impact on the benefit-risk balance, the risk of myopathy including rhabdomyolysis is considered as important potential risk.

ADR=adverse drug reaction; CEC=clinical events committee; CPK=creatine phosphokinase; DILI=drug-induced liver injury; EU=European Union; ; PBC=primary biliary cholangitis; PPARα=peroxisome proliferator-activated receptor α; SmPC=Summary of Product Characteristics; TEAE=treatment emergent adverse event.

Missing Information

The missing information considered important for inclusion as a safety concern in the RMP is presented in Table 14.

Table 14 Missing Information

Missing information	Risk-benefit impact
Long term safety	Long-term safety of elafibranor is an area of missing information as PBC is a chronic disorder and patients are expected to take elafibranor for very long time, probably lifelong (rarity of disorder). The exposure to elafibranor has been limited due to the small number of subjects enrolled in the PBC clinical development programme. Mean duration of exposure to elafibranor 80 mg reported in phase III PBC Study 319-1 was 66.2 weeks (corresponding to 137.2 person-years). Two PBC phase III Studies (GFT505B-319-1; ELATIVE, long term- extension up to 5 years) and (CLIN-60190-454; ELFIDENCE) are ongoing and one phase IV Study (CLIN-60190-461; ELFINITY) is planned as additional pharmacovigilance activities to gain further knowledge on long -term safety of elafibranor.

PBC=primary biliary cholangitis.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable since this is the first RMP for elafibranor.

SVII.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no important identified risks for elafibranor at present. Important potential risks include Hepatic events and Myopathy including rhabdomyolysis, which are presented in Table 15 and Table 16, respectively.

Table 15 Important Potential Risk: Hepatic Events

Hepatic events	
Potential mechanisms:	Biological mechanism is not known. Increase in transaminases is reported with marketed PPARα agonists.
Evidence source(s) and strength of evidence	There was one possible DILI (adjudicated by the CEC) reported in a participant receiving elafibranor in the phase III PBC Study 319-1.
Characterisation of the risk:	A systematic literature review calculated the overall incidence of DILI to be 4.94 per 100,000 persons per year among the general population. This incidence was derived through a systematic review and meta-analysis of published values. The review captured studies up until 01 August 2021 representing multiple sites across multiple countries within Asia, Europe, and America [Li 2023]. Phase III PBC Study 319-1: In the phase III PBC Study 319-1, there was one possible DILI reported in an adult female participant receiving elafibranor, which could have been related to disease progression (patient at risk of disease progression with advanced disease at inclusion). The participant was hospitalised 240 days after elafibranor treatment initiation (on Study Day 240) for hepatic decompensation with ascites and elevated bilirubin, but transaminases remained close to baseline values. During that hospitalisation, oesophageal varices were found on oesophagogastroduodenoscopy and banded. Thereafter, on Study Day 324, she presented with elevated AST of 279 U/L (3.32x baseline value), ALT of 106 U/L (2.52x baseline value) and total bilirubin of 4 mg/dL (3.48x baseline value). These elevations reached protocol-defined thresholds for potential DILI, with permanent study drug discontinuation required. The event was reported as moderate hepatic decompensation (PT Hepatic failure) and was assessed as resolved by the investigator within 24 days, however the total bilirubin remained above the baseline value at the time of the last recorded assessment. The CEC adjudicated the elevation in transaminases and total bilirubin on Study Day 324 as 'possible' DILI, with concurrent medical conditions and concomitant medications unable to be ruled out as potential contributors. Overall, no imbalance was noted in the occurrence of suspected DILI between participants treated with elafibranor (4/108 [3.7%]) and participants treated with placebo (2/53 [3.8%]). A total of 3 cases (1 in the elafibranor group and 2 in the placebo group) of potential DILI were sent for adjudication to the CEC; the elafibranor case was adjudicated as 'possible' DILI, and the 2 placebo cases were adjudicated as 'probable' DILI. Custom MedDRA queries for hepatic failure and hepatic injury identified 4 participants (3.7%) on elafibranor versus 3 participants (5.7%) on placebo with TEAE PTs falling within the Hepatic Failure Custom Query, and 8 participants (7.4%) on elafibranor versus 5 participants (9.4%) on placebo with TEAE PTs falling within the Hepatic Injury Custom Query. The only event reported for >1 participant was blood bilirubin increased: 3 participants (2.8%) in the elafibranor group compared with 1 participant (1.9%) in the placebo group. All other TEAE PTs on custom MedDRA queries for hepatic failure and/or hepatic

Hepatic events	
	injury were reported in a similar proportion of participants between the elafibranor and placebo groups. Phase III NASH Study 315-1: In the phase III NASH Study 315-1, the occurrence rates of adjudicated DILI events were low and comparable between elafibranor and placebo groups. There was a total of 16 positively adjudicated DILI events reported: 11 (0.8%) in the elafibranor group and 5 (0.7%) in the placebo group. None of the 11 participants in the elafibranor treatment arm fulfilled the Hy's law criteria.
Risk factors and risk groups:	Risk factors associated with DILI include age, female gender, pregnancy, daily dose of offending medication including analgesics (acetaminophen), antimicrobials and central nervous system agents (antiepileptic agents, antidepressants, antipsychotics), drugs with high lipophilicity, metabolism characteristics, metabolism genetics, smoking, alcohol consumption, and drug interactions [Chalasani 2008, Li 2022].
Preventability:	Mitigation of this risk and its seriousness/severity can be obtained with an early detection of the liver injury. Clinical and laboratory assessment of liver function should be done prior to initiation of elafibranor treatment and during treatment 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 (EU SmPC Section 4.4).
Impact on the risk-benefit balance of the product	The risk of hepatic events can potentially affect the risk-benefit balance for elafibranor. However, it is anticipated that early detection via regular clinical and laboratory assessment of liver function, which is part of regular routine PBC patient management, and appropriate action taken with elafibranor, can avoid any unfavourable change to the risk-benefit balance.
Public health impact:	As the indication for elafibranor (PBC) is a rare condition and given the low reporting rate of hepatic events during elafibranor clinical development programme, the public health impact of this risk is considered to be low.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CEC=clinical events committee; DILI=drug-induced liver injury; EU=European Union; MedDRA= Medical Dictionary for Regulatory Activities; NASH=nonalcoholic steatohepatitis; PBC=primary biliary cholangitis; PPARα=peroxisome proliferator-activated receptor α; PT=preferred term; SmPC=Summary of Product Characteristics; TEAE=treatment emergent adverse event.

Table 16 Important Potential Risk: Myopathy Including Rhabdomyolysis

Myopathy including rhabdomyolysis	
Potential mechanisms:	Biological mechanism is not known. Increases in CPK and myalgia are reported with marketed PPARα agonists.
Evidence source and strength of evidence:	There was one serious TEAE of rhabdomyolysis reported in a participant receiving elafibranor in the phase III PBC Study 319-1, which was confounded by concomitant intake of atorvastatin. Additionally, as per EU SmPC, blood CPK increased and myalgia are considered as ADRs with elafibranor. Increases in CPK and myalgia have been reported as TEAEs in participants receiving elafibranor in phase III PBC Study 3191 (blood CPK increased: 3.7% in elafibranor group compared to 0% in placebo group; myalgia: 2.8% in elafibranor group compared to 0% in placebo group). Increases in CPK and myalgia are reported with marketed PPARα agonists.
Characterisation of the risk:	The global incidence for myopathy including rhabdomyolysis remains unknown however a French study reported one event over 3 years per 81,301 persons (0.41 per 100,000 persons per year) in the general population of France

Myopathy including rhabdomyolysis	
	[Sgro 2002]. A study in South Korea reported 93 cases of rhabdomyolysis per 143,830 total hospital admissions across 5 years (12.9 per 100,000 persons per year) [Park 2013]. Fibrate administration can lead to myopathy in humans and, in rare scenarios, rhabdomyolysis [Peraza 2006]. Phase III PBC Study 319-1: In the phase III PBC Study 319-1, there was one serious TEAE of rhabdomyolysis resulting in hospitalisation reported in an adult female participant receiving elafibranor (same participant as for the above possible DILI). The event occurred 328 days after elafibranor treatment initiation, and elafibranor treatment was stopped 4 days before the onset of the rhabdomyolysis event. Myoglobinuria result was not available. The participant had been receiving sitagliptin/metformin (Janumet) and atorvastatin, for which rhabdomyolysis is a known adverse drug reaction. Exposure to atorvastatin is increased 11-fold in patients with Child-Pugh B liver cirrhosis [Reference Lipitor Prescribing Information], increasing the risk of rhabdomyolysis. A concomitant event of acute kidney injury was reported (same onset date as for rhabdomyolysis), most probably caused by the rhabdomyolysis. Both rhabdomyolysis and acute kidney injury events resolved within 11 days. Of note, a clinical drug-drug interaction study conducted in healthy participants concluded that coadministration of atorvastatin with steady state elafibranor (180 mg once daily) resulted in 28% lower C_{max} and similar AUC of atorvastatin. Four participants (3.7%) in the elafibranor group had an AESI of blood CPK increased leading to study drug discontinuation per protocol-defined rules, versus no participant in the placebo group. All blood CPK increased events were non-serious and mild or moderate in intensity. No trend was observed in time to onset of these events. Out of these 4 participants, 2 participants had a medical history (autoimmune thyroiditis and chronic kidney disease) and the 2 other participants were taking a concomitant medication (atorvastatin and pravastatin) known to be associated with CPK elevations. In the majority of participants receiving elafibranor, increases in CPK laboratory values were not clinically meaningful. Three participants (2.8%) in the elafibranor group had a TEAE of myalgia, versus no participant in the placebo group. All myalgia events were non-serious and mild or moderate in intensity. No trend was observed in time to onset of these events. Two of these 3 participants also had an AESI of blood CPK increased (participant with autoimmune thyroiditis medical history and participant with concomitant pravastatin medication mentioned above). The remaining participant was also taking a concomitant statin (atorvastatin). Phase III NASH Study 315-1: In the phase III NASH Study 315-1, there was one case of non-serious TEAE of rhabdomyolysis of mild intensity reported in an adult male participant. The event occurred 245 days after elafibranor treatment initiation. CPK were already elevated at baseline (before elafibranor initiation) and increased to 1.5x the baseline value at the time of the rhabdomyolysis event. Myoglobinuria result was not available, and no urine pigmentation or myalgia was reported as such. The participant had a medical history of dyslipidaemia treated with atorvastatin (stopped 107 days before onset of rhabdomyolysis) then ezetimibe, and type 2 diabetes mellitus treated with metformin (ezetimibe and metformin treatments were ongoing at the time of the rhabdomyolysis). Phase II PBC Study 216-1: In the phase II PBC Study 216-1, mean changes in CPK from baseline to end of treatment were +0.3 U/L in elafibranor 80 mg arm, +4.4 U/L in elafibranor

Myopathy including rhabdomyolysis	
	120 mg arm, and –21.9 U/L in placebo arm. No participant had CPK increases that were over the ULN and no cases of myalgia were reported.
Risk factors and risk groups:	Risk factors associated with myopathy including rhabdomyolysis include age (>60 years), comorbidities such as obesity, diabetes, thyroid disorders, alcohol consumption, extended length of surgery, and physical injury/exertion [Chavez 2016, Torres 2015]. Statin drugs have risks including muscle pain, muscle damage, and rhabdomyolysis. Another study in the US reported that the incidence of clinically significant rhabdomyolysis in hospitalised patients occurred in 0.44 per 10,000 (4.4 per 100,000) atorvastatin, simvastatin and pravastatin monotherapy patients [Graham 2004]. This same study also reported that the incidence of rhabdomyolysis in hospitalised patients on statin/fibrate combination therapy was higher than the patients on statin monotherapy [Graham 2004]. PBC patients are commonly exposed to statin drugs as hyperlipidaemia has been seen in up to 80% of patients with PBC [EASL 2017]. The phase III PBC Study 319-1 had an overall 15.5% of participants (25 participants) with hyperlipidaemia reported as medical history, with 19.3% (31 participants) reported to have received a concomitant HMG-CoA reductase inhibitor. The phase II PBC Study 216-1 had an overall 17.8% of participants (8 participants) with hyperlipidaemia reported as medical history, with 22.2% (10 participants) reported to have received a concomitant HMG-CoA reductase inhibitor.
Preventability:	Mitigation of this risk and its seriousness/severity can be obtained with an early detection of blood CPK increase and prompt reporting of myalgia events. CPK should be evaluated prior to treatment initiation and thereafter according to routine patient management. Periodic CPK measurements may be considered in patients starting elafibranor treatment, especially those on concomitant HMG-CoA reductase inhibitors. If increases in CPK or unexplained signs and symptoms of muscle injury are observed, prompt investigation of the cause is recommended and interruption of elafibranor treatment should be considered (EU SmPC Section 4.4).
Impact on the risk-benefit balance of the product	The risk of myopathy including rhabdomyolysis can potentially affect the -benefit risk balance for elafibranor. However, it is anticipated that early detection via CPK measurements (at elafibranor initiation and thereafter according to routine patient management) with increased vigilance in patients taking concomitant statins, and appropriate action taken with elafibranor and any suspected concomitant drug, can avoid any unfavourable change to the risk-benefit balance.
Public health impact:	As the indication for elafibranor (PBC) is a rare condition and given the low reporting rate of myopathy including rhabdomyolysis during elafibranor clinical development programme, the public health impact of this risk is considered to be low.

ADR=adverse drug reaction; AESI=adverse event of special interest; AUC=area under curve; C_{max}=maximum concentration; CPK=creatine phosphokinase; DILI=drug-induced liver injury; EASL=European Association for the Study of the Liver; EU=European Union; HMG-CoA=3-hydroxy-3-methyl-glutaryl-coenzyme A; NASH=nonalcoholic steatohepatitis; PBC=primary biliary cholangitis; PPARα=peroxisome proliferator-activated receptor α; SmPC=Summary of Product Characteristics; TEAE=treatment emergent adverse event; ULN=upper limit of normal; US=United States.

SVII.3.2 Presentation of the Missing Information

Missing information includes Long-term safety which is presented in Table 17.

Table 17 Missing Information: Long Term Safety

LongTerm Safety	
Evidence source:	Long-term safety of elafibranor is an area of missing information as PBC is a chronic disorder and patients are expected to take elafibranor for very long time, probably lifelong (rarity of disorder). The exposure to elafibranor has been limited due to the small number of subjects enrolled in the PBC clinical development programme. Mean duration of exposure to elafibranor 80 mg reported in phase III PBC Study 319-1 was 66.2 weeks (corresponding to 137.2 person -years). Population in need of further characterisation: Due to limited exposure of elafibranor in the clinical development programme, current available data are not sufficient to describe the long-term safety of the product. Two PBC phase III Studies (GFT505B-319-1; ELATIVE, long -term extension up to 5 years) and (CLIN-60190-454; ELFIDENCE) are ongoing and one phase IV Study (CLIN-60190-461; ELFINITY) is planned as additional pharmacovigilance activities to gain further knowledge on long -term safety of elafibranor.

PBC=primary biliary cholangitis.

Part II: Module SVIII – Summary of the Safety Concerns

Table 18 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Hepatic events • Myopathy including rhabdomyolysis
Missing information	• Long term safety

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are presented below.

Specific adverse reaction follow-up questionnaires

Targeted safety follow-up questionnaires have been developed for elafibranor important potential risks: hepatic events and muscle injury events (Annex 4). These questionnaires will be sent to the reporter of post-marketing safety cases with the objective to collect all the relevant data for risk characterisation.

Other forms of routine pharmacovigilance activities

Not applicable. There are no other routine pharmacovigilance activities for elafibranor.

III.2 Additional Pharmacovigilance Activities

The ongoing and proposed additional pharmacovigilance activities are presented below.

ELATIVE Phase III Study (GFT505B-319-1): A double-blind, long term extension study to evaluate the efficacy and safety of elafibranor in patients with PBC.

Study short name and title:

A Double-blind, Randomised, Placebo-Controlled and Open label Long- -Term Extension Study to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid.

The DBP is completed, and long -term extension (LTE) is ongoing.

Rationale and study objectives:

The main aim of this study is to determine if elafibranor is better than placebo at decreasing levels of ALP and normalisation of total bilirubin (TB) that provides information about participant's disease. This study will also study the safety of long-term treatment with elafibranor, as well as the impact on symptoms such as pruritus and fatigue.

Primary objectives:

- The objective of the first part of this study (ie, DBP) is to evaluate the effect of elafibranor (80 mg/day) on cholestasis as defined by the primary endpoint response to treatment at Week 52 defined as ALP <1.67 x ULN and TB ≤ULN and ALP decrease ≥5%.
- 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 DBP.

Key secondary objectives:

- To evaluate the effect of elafibranor (80 mg/day) over 52 weeks of treatment compared to placebo on:
  - Normalisation of ALP
  - Pruritus based on change from baseline through Week 52 in PBC Worst Itch numeric rating scale (NRS) in patients with baseline PBC Worst Itch NRS score ≥4
  - Pruritus based on change from baseline through Week 24 in PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4.

Study design:

This is a phase III double-blind, randomised, placebo-controlled study with an open-label long-term extension (LTE) evaluating the efficacy and safety of elafibranor 80 mg once daily versus placebo in patients with PBC and inadequate response or intolerance to UDCA.

In the DBP, patients were randomised in a 2:1 ratio to receive elafibranor 80 mg or placebo, once daily. The DBP lasted until the last completed Week 52 (visit 6) or until a maximum of 104 weeks DBP, whichever happened first, to further collect safety and clinical outcomes data in a DB manner. After the DBP, all patients will receive elafibranor 80 mg daily for up to 5 years or until the patient's total treatment duration is 6 years, whichever occurs first during the LTE period.

When applicable, patients should continue their pre-study dose of UDCA throughout the study participation.

Study population:

This study includes patients with PBC with inadequate response or intolerance to UDCA. Partial or suboptimal responders constitute up to 40% of UDCA-treated PBC patients [Ali 2015]. This group of patients along with patients intolerant to UDCA treatment will be randomised in this study. This study

targets patients with mild and moderately advanced disease and excludes patients with advanced cirrhosis.

Milestones:

Protocol submission: 17 August 2020 (actual date)

Planned Final report: November 2028.

ELFIDENCE Phase III Study (CLIN-60190-454): A double-blind study to evaluate the efficacy and safety of elafibranor on long term clinical outcomes in patients with PBC.

Study short name and title:

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).

Rationale and study objectives:

The main aim of this confirmatory study is to determine if elafibranor is better than placebo in preventing clinical outcome events showing disease worsening (including progression of disease leading to liver transplant or death) to convert the conditional approval into a standard marketing authorisation once the Marketing Authorisation Holder obligations are fulfilled. This study will also study the safety of long-term treatment with elafibranor, as well as the impact on symptoms such as pruritus and fatigue.

Primary objective:

- To evaluate the efficacy of daily oral administration of elafibranor 80 mg compared to placebo based on time to the occurrence of clinical outcome events in adult participants with PBC and cirrhosis.

Secondary objectives:

- To assess the safety and tolerability of daily long-term oral administration of elafibranor 80 mg compared to placebo in adult participants with PBC and cirrhosis.
- To evaluate the efficacy of daily oral administration of elafibranor 80 mg compared to placebo in adult participants with PBC and cirrhosis on efficacy measures, including:
    - Biochemical and clinical markers of response
    - Disease-related symptoms
    - Patient report outcomes including other disease-related symptoms, and quality of life (QoL)
    - Individual components of the composite primary endpoint and liver-related mortality.
- To evaluate the PK of elafibranor and its metabolite GFT1007 in adult participants with PBC and cirrhosis using a Population PK approach, including identification of covariates impacting PK variability.

Study design:

This is a phase III, randomised, double-blind, multicentre, parallel-group study to evaluate the safety and efficacy of elafibranor 80 mg compared with placebo in male and female participants aged 18 years or more with PBC and cirrhosis (Child Pugh A and B).

This study is designed to include two interim analyses. The first interim analysis for efficacy per the primary endpoint will be after 34 adjudicated clinical outcome events (50% information fraction) have occurred in distinct participants.

The second interim analysis for efficacy and futility will be after 50 adjudicated clinical outcome events (75% information fraction) have occurred in distinct participants. If the study is not stopped for efficacy or futility at the time of either of the interim analyses, it will continue to the final analysis which will occur after 67 adjudicated clinical events in distinct participants have occurred.

Study population:

The study population will consist of participants with PBC, with inadequate response or intolerance to UDCA as defined by the inclusion and exclusion criteria. Per protocol, participants with cirrhosis Child Pugh A or Child Pugh B will be eligible to enroll.

Milestones:

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.

ELFINITY Phase IV Study (CLIN-60190-461): Non-interventional study to assess the effectiveness, safety and tolerability of elafibranor in patients with PBC.

Study short name and title:

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.

Rationale and study objectives:

This study aims 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 60 months to assess effectiveness and safety of elafibranor and its impact on patients' QoL as part of additional pharmacovigilance activities to further assess the effectiveness and safety of elafibranor in a real-world setting.

Primary objective:

- To evaluate the effectiveness of elafibranor on cholestasis at six months after starting treatment.

Secondary objectives:

-
- To evaluate the effectiveness of elafibranor at various timepoints throughout the 60-months treatment period on:
  - Alkaline phosphatase (ALP);
  - Cholestasis;
  - Liver function parameters;

  - Pruritus;
  - Fatigue;
  - Sleep;
  - Quality of Life (QoL);
  - Progression of liver stiffness.
- To evaluate the effectiveness of elafibranor on time to the occurrence of clinical outcome events;
- To evaluate safety and tolerability of elafibranor;
- To evaluate patient's satisfaction with elafibranor treatment;
- To describe patient's adherence to treatment.

•

Study design:

This is an international, multicentre, prospective, noninterventional, phase IV study. Adult patients with PBC for whom the treating physician has decided to start treatment with elafibranor 80 mg/day, as recommended in the approved indication, will be followed up according to routine clinical practice over a period of 60 months (5 years). Patients will receive elafibranor as prescribed by their treating physician and according to the SmPC/Prescribing Information (PI) and/or according to the marketing authorisation, which may include elafibranor in combination with UDCA or as monotherapy. The decision to prescribe elafibranor will be made prior to and independently of the decision to enroll the patient in this study.

Interim analysis will be performed once a year, if relevant, in consultation with the Study Steering Committee. The first interim analysis will be planned when 50 patients have completed their three months of treatment with elafibranor (80 mg/day).

Study population:

The study aims to enroll 424 patients with PBC for whom the treating physician has decided to start treatment with elafibranor 80 mg/day, as recommended in the approved indication which may include elafibranor in combination with UDCA or as monotherapy. A minimum of 12 patients with PBC treated with elafibranor as monotherapy will be recruited.

Milestones:

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.

III.3 Summary Table for Additional Pharmacovigilance Activities

Table 19 Summary of Ongoing and Planned Additional Pharmacovigilance 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)	The objective of this confirmatory phase III	• Hepatic events	Protocol submission	29 September 2023 (actual date)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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)	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.	• Myopathy including rhabdomyolysis • Long term safety	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
Phase IV Study (CLIN-60190-461) Prospective Non Interventional, Phase IV Multicentre Study to Assess the	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 with UDCA or as monotherapy as	• Hepatic events • Myopathy including rhabdomyolysis • Long term safety	Planned Protocol submission	09 April 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Effectiveness, Safety and Tolerability of Elafibranor 80 mg/day in Patients with Primary Biliary Cholangitis Receiving Treatment in a Real-World Setting. (Planned)	recommended in the approved indication, over a period of 60 months to assess effectiveness and safety of elafibranor and its impact on patients' QoL.		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.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 20 Planned and Ongoing Post-authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies 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 standart marketing authorisation and to evaluate the long-term clinical outcomes and long-term safety of elafibranor 80 mg in participants with PBC and cirrhosis.	Efficacy on long term clinical outcomes	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

PBC=primary biliary cholangitis.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Table 21 summarises the routine risk minimisation measures in place for the safety concerns.

Table 21 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. 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.

CPK=creatinine phosphokinase; EU=European Union; HMG-CoA=3-hydroxy-3-methyl-glutaryl-coenzyme A; SmPC=Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

There are no planned or ongoing additional risk minimisation measures for elafibranor at present. Routine risk minimisation activities as described in V.1 Routine Risk Minimisation Measures are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 22 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatic events	Routine risk minimisation measures: EU SmPC Section 4.4: Special warnings and precautions for use Package leaflet Section 2 Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse event targeted follow-up questionnaire to collect relevant safety data Additional pharmacovigilance activities: Ongoing studies: ELATIVE Phase III Study (GFT505B-319-1) Planned final report: November 2028 ELFIDENCE Phase III Study (CLIN-60190-454) Planned final report: May 2030 Planned study: ELFINITY Phase IV Study (CLIN-60190-461) Planned final report: December 2032
Myopathy including rhabdomyolysis	Routine risk minimisation measures: EU SmPC Section 4.4: Special warnings and precautions for use Package leaflet Section 2 Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse event targeted follow-up questionnaire to collect relevant safety data Additional pharmacovigilance activities: Ongoing studies: ELATIVE Phase III Study (GFT505B-319-1) Planned final report: November 2028 ELFIDENCE Phase III Study (CLIN-60190-454) Planned final report: May 2030 Planned study: ELFINITY Phase IV Study (CLIN-60190-461) Planned final report: December 2032
Long-term safety	Routine risk minimisation measures: None Other routine risk minimisation measures beyond the Product Information:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Medicine's legal status: Prescription only medicine Additional risk minimisation measures: None	Ongoing studies: ELATIVE Phase III Study (GFT505B-319-1) Planned final report: November 2028 ELFIDENCE Phase III Study (CLIN-60190-454) Planned final report: May 2030 Planned study: ELFINITY Phase IV Study (CLIN-60190-461) Planned final report: December 2032

EU=European Union; SmPC=Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for IQIRVO (elafibranor)

This is a summary of the RMP for IQIRVO. The RMP details important risks of IQIRVO, how these risks can be minimised and how more information will be obtained about IQIRVO's risks and uncertainties (missing information).

IQIRVO's EU SmPC and its package leaflet gives essential information to healthcare professionals and patients on how IQIRVO should be used.

This summary of the RMP for IQIRVO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates to IQIRVO's RMP.

I. The Medicine and What is it Used for

IQIRVO is authorised for the treatment of primary biliary cholangitis in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. It contains elafibranor as the active substance and it is given by oral administration.

Further information about the evaluation of IQIRVO’s benefits can be found in the EPAR, including in its plain-language summary, available on the EMA website under the medicine’s webpage Medicines European Medicines Agency (europa.eu).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of IQIRVO, together with measures to minimise such risks and the proposed studies for learning more about IQIRVO's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and EU SmPC addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine’s legal status — the way medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of IQIRVO is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of IQIRVO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of IQIRVO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	• Hepatic events • Myopathy including rhabdomyolysis
Missing information	• Long-term safety

II.B Summary of Important Risks

Important Potential Risks

Hepatic events	
Evidence for linking the risk to the medicine	There was one possible DILI reported in a clinical trial participant receiving elafibranor, who was at risk of disease progression (advanced disease at inclusion).
Risk factors and risk groups	Risk factors associated with DILI include age, female gender, pregnancy, daily dose of offending medication including analgesics (acetaminophen), antimicrobials and central nervous system agents (antiepileptic agents, antidepressants, antipsychotics), drugs with high lipophilicity, metabolism characteristics, metabolism genetics, smoking, alcohol consumption and drug interactions.
Risk minimisation measures	Routine risk minimisation measures: EU SmPC Section 4.4 Package leaflet Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Ongoing studies: ELATIVE Phase III Study (GFT505B-319-1) ELFIDENCE Phase III Study (CLIN-60190-454) Planned study: ELFINITY Phase IV Study (CLIN-60190-461) See section II.C of this summary for an overview of the post-authorisation development plan.

Myopathy including rhabdomyolysis	
Evidence for linking the risk to the medicine	There was one serious event of rhabdomyolysis reported in a clinical trial participant receiving elafibranor, who was concomitantly treated with a statin drug, atorvastatin, for which rhabdomyolysis is a known adverse drug reaction. This participant was the same as for the above-mentioned possible DILI. Additionally, as per EU SmPC, blood CPK increased and myalgia are considered as ADRs with elafibranor. Increases in CPK and myalgia have been reported as TEAEs in participants receiving elafibranor in phase III PBC Study 3191 (blood CPK increased: 3.7% in elafibranor group compared to 0% in placebo group; myalgia: 2.8% in elafibranor group compared to 0% in placebo group). Increases in CPK and myalgia are reported with marketed PPARα agonists.
Risk factors and risk groups	Risk factors associated with myopathy including rhabdomyolysis include age (>60 years), comorbidities such as obesity, diabetes, thyroid disorders, alcohol consumption extended length of surgery, and physical injury/exertion. Statin drugs have risk including muscle pain, muscle damage, and rhabdomyolysis. PBC patients are commonly exposed to statin drugs as hyperlipidaemia has been seen in up to 80% of patients with PBC.
Risk minimisation measures	Routine risk minimisation measures: EU SmPC Section 4.4 Package leaflet Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Ongoing studies: ELATIVE Phase III Study (GFT505B-319-1) ELFIDENCE Phase III Study (CLIN-60190-454) Planned study: ELFINITY Phase IV Study (CLIN-60190-461) See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information

Missing Information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Ongoing studies: ELATIVE Phase III Study (GFT505B-319-1) ELFIDENCE Phase III Study (CLIN-60190-454) Planned study: ELFINITY Phase IV Study (CLIN-60190-461) See section II.C of this summary for an overview of the post-authorisation development plan.

ADR=adverse drug reaction; CPK=creatine phosphokinase; DILI=drug-induced liver injury; EU=European Union; PBC=primary biliary cholangitis; PPARα=peroxisome proliferator-activated receptor α; SmPC=Summary of Product Characteristics; TEAE=treatment emergent adverse event.

II.C Post-authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is the condition of marketing authorisation:

- ELFIDENCE Phase III Study (CLIN-60190-454)

Purpose of the study:

The purpose of this confirmatory phase III study is to confirm the efficacy and safety of elafibranor (via assessment of the long-term clinical outcomes) to convert the conditional approval into a standard marketing authorisation once the Marketing Authorisation Holder obligations are fulfilled and and to evaluate long -term safety of elafibranor 80 mg in participants with PBC.

II.C.2 Other studies in post-authorisation development plan

- ELATIVE Phase III Study (GFT505B-319-1)

Purpose of the study:

The purpose of the second part of this study (ie, 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 DBP.

- ELFINITY Phase IV Study (CLIN-60190-461)

Purpose of the study:

The purpose 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.

Annex 4 – Specific Adverse Drug Reaction Follow-up Forms

Targeted safety follow-up questionnaires are used to collect relevant safety data related to the important potential risks.

Adverse events	Title (internal reference) of the questionnaire
Hepatic events	Targeted Safety Follow-up Questionnaire for elafibranor / HEPATIC EVENTS (432404-FOR)
Muscle injury events	Targeted Safety Follow-up Questionnaire for elafibranor / MUSCLE INJURY (432405-FOR)

Targeted Safety Follow-up Questionnaire for HEPATIC EVENTS

Associated Procedure / Instruction Ref:	337504-SOP
Form reference & Version	432404-FOR V4.0

TARGETED SAFETY FOLLOW-UP QUESTIONNAIRE FOR ELAFIBRANOR / HEPATIC EVENTS

You have received this questionnaire because you have reported a hepatic event with elafibranor. Please provide as much information as available to you and attach additional pages of relevant information as necessary. Please tick the box where applicable and fill in dates in the following format: DD/MMM/YYYY.

Any personal data you share with Ipsen will be protected and processed in line with applicable privacy and data laws, including the European Union General Data Protection Regulation (GDPR), and any other applicable local laws that regulate the storage, processing, access and transfer of personal data. The information you provide will be used for the purpose of monitoring the safety of Ipsen's products and may be shared with health authorities to meet relevant legal obligations. To understand how we process your data or how to exercise your rights, please read our Privacy Notice: https://www.ipsen.com/global-privacy-policy/adverse-events-product-quality-complaints-or-medical-information-enquiries/

IPSEN use only			
Manufacturer's Control Number (MCN):	☐ Initial	☐ Follow-up	Date of Notification:
Study Number (if applicable):	Patient Number (if applicable):		Date of Initial Notification:

Patient Information:		
Patient's Initials:	Date of birth: __/___/____	Age: years
Sex: ☐ Male ☐ Female	Current height: cm	Current weight: kg

Product information: Please provide the following information on elafibranor suspect product

Product	Indication	Dose	Frequency	Form / Route	Start date	Stop date / ongoing
Elafibranor					__/___/____	__/___/____ ☐ Ongoing

Product information: Please list all concomitant medications and provide the following information – Please note all relevant medications the patient was taking at the time of the event(s) (including prescribed or over-the-counter medications, herbal products, supplements, and/or vitamins) and indicate for each medication whether it was suspect (i.e., whether it may have contributed to the hepatic event(s))

	Product (brand name if known or generic)	Suspect? (Yes/No)	Indication	Dose	Frequency	Form / Route	Start date	Stop date / ongoing
1		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
2		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing

Product information: Please list all concomitant medications and provide the following information – Please note all relevant medications the patient was taking at the time of the event(s) (including prescribed or over-the-counter medications, herbal products, supplements, and/or vitamins) and indicate for each medication whether it was suspect (i.e., whether it may have contributed to the hepatic event(s))

	Product (brand name if known or generic)	**Suspect?** (Yes/No)	**Indication**	**Dose**	**Frequency**	**Form / Route**	**Start date**	**Stop date / ongoing**
3		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing
4		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing
5		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing
6		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing

Event information: Please list the hepatic event(s) and all other relevant event(s) experienced by the patient at the time of the hepatic event(s) and provide the following information

	Event(s) (Please describe the clinical course in the 'Narrative' section)	**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality** for each suspect product**
1		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to elafibranor, please provide alternative etiology(ies):
2		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged)	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s):

Event information: Please list the hepatic event(s) and all other relevant event(s) experienced by the patient at the time of the hepatic event(s) and provide the following information							
	Event(s) (Please describe the clinical course in the 'Narrative' section)	**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality** for each suspect product**
		☐ Other medically important condition ☐ Non-serious					If not related to elafibranor, please provide alternative etiology(ies):
3		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to elafibranor, please provide alternative etiology(ies):
4		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to elafibranor, please provide alternative etiology(ies):
5		☐ Death	__/___/____	☐ Fatal*	__/___/____	☐ Yes	☐ Related

Event information: Please list the hepatic event(s) and all other relevant event(s) experienced by the patient at the time of the hepatic event(s) and provide the following information							
Event(s) (Please describe the clinical course in the 'Narrative' section)		**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality** for each suspect product**
		☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious		☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	☐ Ongoing	☐ No If yes, please provide details:	Suspect product(s): ☐ Not related Suspect product(s): If not related to elafibranor, please provide alternative etiology(ies):

*Please provide the autopsy report, if available. **Please provide the relationship between the event and each of the suspect products.

Action taken information: Please provide the following details for elafibranor and any other suspect product(s)				
Product	**Action taken with the suspect product in response to the hepatic event(s)**	**Date of action taken** (if applicable)	**Did the hepatic event(s) resolve following this action?** (Yes/No)	**If the product was re-introduced, did the hepatic event(s) re-occur (positive rechallenge)?**
Elafibranor	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)

Action taken information: Please provide the following details for elafibranor and any other suspect product(s)				
Product	**Action taken with the suspect product in response to the hepatic event(s)**	**Date of action taken** (if applicable)	**Did the hepatic event(s) resolve following this action?** (Yes/No)	**If the product was re-introduced, did the hepatic event(s) re-occur (positive rechallenge)?**
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/___	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/___	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/___	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)

Patient's Medical History: Please provide any relevant medical history information including any pre-existing hepatic disorders prior to initiation of elafibranor treatment (specifying start (diagnosis) and end dates, if available)	
Current (ongoing)	
Previous	

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the hepatic event(s) (including baseline results prior to elafibranor initiation, if available)			
Test / examination name	**Test / examination date**	**Test / examination result**	**Normal range** (if applicable)
Blood alkaline phosphatase (ALP)			
Total bilirubin (TB)			
Direct (conjugated) bilirubin (DB)			
Blood albumin			
Aspartate aminotransferase (AST)			
Alanine aminotransferase (ALT)			
Gamma-glutamyl transferase (GGT)			

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the hepatic event(s) (including baseline results prior to elafibranor initiation, if available)			
Complete blood count (CBC)			
C reactive protein (CRP)			
Viral serology			
Gamma globulin (Immunoglobulin G (IgG))			
Prothrombin time (PT)			
International normalized ratio (INR)			
Liver ultrasound			
Liver scan			
Liver biopsy			
Any other relevant test / examination			

Please attach any relevant examination report.

Narrative: Please describe the clinical course of the hepatic event(s)

Additional queries	
What was the stage of the liver disease treated with elafibranor at the time of elafibranor initiation (including fibrosis and cirrhosis stages)?	
What was the stage of the liver disease treated with elafibranor at the time of (or at the closest available time to) the occurrence of the above-reported hepatic event(s) (including fibrosis and cirrhosis stages)?	
Did the patient experience any of the following signs and symptoms of hepatic decompensation at the time of (or close to) the occurrence of the above-reported hepatic event(s)? If yes, please provide details in the appropriate sections ('Event information', 'Investigations' and 'Narrative').	Jaundice: ☐ Yes ☐ No MELD-Na score ≥ 12: ☐ Yes ☐ No Hepatorenal syndrome: ☐ Yes ☐ No Ascites: ☐ Yes ☐ No Variceal bleeds: ☐ Yes ☐ No Hepatic encephalopathy: ☐ Yes ☐ No Spontaneous bacterial peritonitis: ☐ Yes ☐ No
Has the patient experienced any recent infection(s)? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any alcohol or substance abuse issues? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any of the following medical history? If yes, please provide details in the appropriate section ('Patient's Medical History').	Jaundice: ☐ Yes ☐ No MELD-Na score ≥ 12: ☐ Yes ☐ No Hepatorenal syndrome: ☐ Yes ☐ No Ascites: ☐ Yes ☐ No Variceal bleeds: ☐ Yes ☐ No Hepatic encephalopathy: ☐ Yes ☐ No Spontaneous bacterial peritonitis: ☐ Yes ☐ No
Does the patient have any family history of liver disease? If yes, please provide details.	

Reporter's details	
Name:	Signature:

Targeted Safety Follow-up Questionnaire for MUSCLE INJURY EVENT

Associated Procedure / Instruction Ref:	337504-SOP
Form reference & Version:	432405-FOR V3.0

TARGETED SAFETY FOLLOW-UP QUESTIONNAIRE FOR ELAFIBRANOR / MUSCLE INJURY

You have received this questionnaire because you have reported muscle injury with elafibranor. Please provide as much information as available to you and attach additional pages of relevant information as necessary. Please tick the box where applicable and fill in dates in the following format: DD/MMM/YYYY.

Any personal data you share with Ipsen will be protected and processed in line with applicable privacy and data laws, including the European Union General Data Protection Regulation (GDPR), and any other applicable local laws that regulate the storage, processing, access and transfer of personal data. The information you provide will be used for the purpose of monitoring the safety of Ipsen's products and may be shared with health authorities to meet relevant legal obligations. To understand how we process your data or how to exercise your rights, please read our Privacy Notice: https://www.ipsen.com/global-privacy-policy/adverse-events-product-quality-complaints-or-medical-information-enquiries/

IPSEN use only			
Manufacturer's Control Number (MCN):	☐ Initial	☐ Follow-up	Date of Notification:
Study Number (if applicable):	Patient Number (if applicable):		Date of Initial Notification:

Patient Information:		
Patient's Initials:	Date of birth: __/___/____	Age: years
Sex: ☐ Male ☐ Female	Current height: cm	Current weight: kg

Product information: Please provide the following information on elafibranor suspect product

Product	Indication	Dose	Frequency	Form / Route	Start date	Stop date / ongoing
Elafibranor					__/___/____	__/___/____ ☐ Ongoing

Product information: Please list all concomitant medications and provide the following information – Please note all relevant medications the patient was taking at the time of the event(s) (including prescribed or over-the-counter medications, herbal products, supplements, and/or vitamins) and indicate for each medication whether it was suspect (i.e., whether it may have contributed to the muscle-related event(s))

	Product (brand name if known or generic)	Suspect? (Yes/No)	Indication	Dose	Frequency	Form / Route	Start date	Stop date / ongoing
1		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing
2		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing

Product information: Please list all concomitant medications and provide the following information – Please note all relevant medications the patient was taking at the time of the event(s) (including prescribed or over-the-counter medications, herbal products, supplements, and/or vitamins) and indicate for each medication whether it was suspect (i.e., whether it may have contributed to the muscle-related event(s))

	Product (brand name if known or generic)	**Suspect?** (Yes/No)	**Indication**	**Dose**	**Frequency**	**Form / Route**	**Start date**	**Stop date / ongoing**
3		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing
4		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing
5		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing
6		☐ Yes ☐ No					__/___/__ —	__/___/____ ☐ Ongoing

Event information: Please list the muscle-related event(s) and all other relevant event(s) experienced by the patient at the time of the muscle-related event(s) and provide the following information

	Event(s) (Please describe the clinical course in the 'Narrative' section)	**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality** for each suspect product**
1		☐ Death ☒ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to elafibranor, please provide alternative etiology(ies):
2		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new)	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s):

Event information: Please list the muscle-related event(s) and all other relevant event(s) experienced by the patient at the time of the muscle-related event(s) and provide the following information							
	Event(s) (Please describe the clinical course in the 'Narrative' section)	**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality** for each suspect product**
		☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious					If not related to elafibranor, please provide alternative etiology(ies):
3		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to elafibranor, please provide alternative etiology(ies):
4		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to elafibranor, please provide alternative etiology(ies):
5		☐ Death ☐ Life-threatening	__/___/____	☐ Fatal* ☐ Not recovered / Resolved	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s):

Event information: Please list the muscle-related event(s) and all other relevant event(s) experienced by the patient at the time of the muscle-related event(s) and provide the following information							
Event(s) (Please describe the clinical course in the 'Narrative' section)		**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality** for each suspect product**
		☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalisation (new) ☐ Hospitalisation (prolonged) ☐ Other medically important condition ☐ Non-serious		☐ Recovering / Resolving ☐ Recovered with sequelae ☐ Unknown			☐ Not related Suspect product(s): If not related to elafibranor, please provide alternative etiology(ies):

*Please provide the autopsy report, if available. **Please provide the relationship between the event and each of the suspect products.

Action taken information: Please provide the following details for elafibranor and any other suspect product(s)				
Product	**Action taken with the suspect product in response to the muscle-related event(s)**	**Date of action taken** (if applicable)	**Did the muscle-related event(s) resolve following this action?** (Yes/No)	**If the product was re-introduced, did the muscle-related event(s) re-occur (positive rechallenge)?**
Elafibranor	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)

Action taken information: Please provide the following details for elafibranor and any other suspect product(s)				
Product	**Action taken with the suspect product in response to the muscle-related event(s)**	**Date of action taken** (if applicable)	**Did the muscle-related event(s) resolve following this action?** (Yes/No)	**If the product was re-introduced, did the muscle-related event(s) re-occur (positive rechallenge)?**
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
	☐ Continued without change ☐ Dose decreased ☐ Interrupted ☐ Permanently discontinued	__/__/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)

Patient's Medical History: Please provide any relevant medical history information including any pre-existing muscle-related disorders prior to initiation of elafibranor treatment (specifying start (diagnosis) and end dates, if available)	
Current (ongoing)	
Previous	

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the muscle-related event(s) (including baseline results prior to elafibranor initiation, if available)			
Test / examination name	**Test / examination date**	**Test / examination result**	**Normal range** (if applicable)
Blood creatine phosphokinase (CPK)			
Urine myoglobin			
Complete blood count (CBC)			
Blood urea nitrogen (BUN)			
Blood creatinine			
Blood glucose			
Blood calcium			
Blood potassium			
Blood phosphate			
Blood sodium			

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the muscle-related event(s) (including baseline results prior to elafibranor initiation, if available)			
Blood chloride			
Uric acid			
Liver function tests (LFTs)			
Thyroid tests			
Blood albumin and total proteins			
Blood aldolase			
Lactate dehydrogenase (LDH)			
Estimated glomerular filtration rate (eGFR)			
Electrocardiogram (ECG)			
Any other relevant test / examination			

Please attach any relevant examination report.

Narrative: Please describe the clinical course of the muscle-related event(s)

Additional queries	
Did the patient experience any of the following signs and symptoms at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate sections ('Event information', 'Investigations' and 'Narrative').	Myalgia: ☐ Yes ☐ No Generalized muscle weakness: ☐ Yes ☐ No Muscle swelling: ☐ Yes ☐ No Muscle tenderness: ☐ Yes ☐ No Marked increase in muscle CPK values: ☐ Yes ☐ No Myoglobinuria: ☐ Yes ☐ No Urine pigmentation (darkened urine): ☐ Yes ☐ No Fever: ☐ Yes ☐ No Nausea: ☐ Yes ☐ No Vomiting: ☐ Yes ☐ No
Were there any signs of rhabdomyolysis complications (including acute kidney injury)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative').	☐ Yes ☐ No
Was the patient practicing a sustained physical activity of high intensity at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate section ('Narrative').	☐ Yes ☐ No
Did the patient experience any traumatic injuries (e.g., fall) before or at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative') including circumstances/cause.	☐ Yes ☐ No
Did the patient experience any hyperthermia or hypothermia at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative').	Hyperthermia: ☐ Yes ☐ No Hypothermia: ☐ Yes ☐ No
Was the patient taking any statins at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate section ('Product information').	☐ Yes ☐ No

Additional queries	
Has the patient experienced any recent infection(s)? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any alcohol or substance abuse issues? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any of the following medical history? If yes, please provide details in the appropriate section ('Patient's Medical History').	

Myalgia	☐ Yes ☐ No
Generalized muscle weakness	☐ Yes ☐ No
Muscle swelling	☐ Yes ☐ No
Muscle tenderness	☐ Yes ☐ No
Marked increase in muscle CPK values	☐ Yes ☐ No
Myoglobinuria	☐ Yes ☐ No
Urine pigmentation (darkened urine)	☐ Yes ☐ No
Rhabdomyolysis	☐ Yes ☐ No
Inflammatory myopathy	☐ Yes ☐ No
Muscular dystrophy	☐ Yes ☐ No
Other chronic muscle disease If yes, please specify:	☐ Yes ☐ No
Muscle phosphorylase deficiency	☐ Yes ☐ No
Other enzyme deficiency If yes, please specify:	☐ Yes ☐ No

Reporter's details	
Name:	Signature:

Annex 6 - Details of Proposed Additional Risk Minimisation Activities

Not applicable.

Annex 7 - Other Supporting Data (including referenced material)

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