25 February 2021
EMA/CHMP/105411/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemazyre

International non-proprietary name: pemigatinib

Procedure No. EMEA/H/C/005266/0000

Note

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

Administrative information

Name of the medicinal product:	Pemazyre
Applicant:	Incyte Biosciences Distribution B.V. Paasheuvelweg 25 1105 BP Amsterdam NETHERLANDS
Active substance:	PEMIGATINIB
International Non-proprietary Name/Common Name:	pemigatinib
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents, protein kinase inhibitors (L01EX20)
Therapeutic indication(s):	Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.
Pharmaceutical form(s):	Tablet
Strength(s):	4.5 mg, 9 mg and 13.5 mg
Route(s) of administration:	Oral use
Packaging:	blister (Aclar/PVC/paper/Alu)
Package size(s):	14 tablets and 28 tablets

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List of abbreviations

ALT	Alanine aminotransferase
AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	Aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC0-24	area under the plasma concentration-time curve from Hour 0 to 24
AUC0-∞	area under the plasma concentration-time curve extrapolated to time of infinity
BBB	blood-brain barrier
BCRP	breast cancer resistant protein
BCS	Biopharmaceutics Classification System
BDL	Below the limit of detection
b-FGF	basic fibroblast growth factor
BID	twice daily
BOR	Best overall response
BUN	Urea nitrogen
CEP	Certificate of Suitability of the EP
CFU	Colony forming units
CHMP	Committee for Medicinal Products for Human use
Cmax	maximum observed plasma concentration
CMS	Concerned Member State
CoA	Certificate of Analysis
CQA	Critical quality attribute
CRS	Chemical reference substance
CYP	cytochrome P450
DDI	drug-drug interaction
DL	Detection Limit
DLT	dose-limiting toxicity
DMAC	dimethylacetamide
DMB	Drug Metabolism and Biopharmaceutics
DMF	Dimethylformamide
DMF	Drug Master File = Active Substance Master File
DNA	deoxyribonucleic acid
DoE	Design of experiments
DOM	Date of manufacture
DRF	Dose-range finding
DSC	Differential scanning Calorimetry
DVS	Dynamic vapour sorption
EC	European Commission
ECD	Electrochemical detection
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EGFR	epidermal growth factor receptor
EP	European Pharmacopoeia
FaSSIF	Fasted state simulated intestinal fluid
FDA	Food and Drug Administration
FeSSIF	Fed state simulated intestinal fluid
FGF	fibroblast growth factor
FGFR	Fibroblast Growth Factor Receptor
FID	Flame ionisation detection
FT-IR	Fourrier transmission infra red (spectroscopy)
fu	fraction unbound
GC	Gas chromatography

GFR	glomerular filtration rate
GGT	Glutamyl transferase
GLP	Good Laboratory Practices
GSH	glutathione
HDPE	High Density Polyethylene
HED	Human equivalent dose
hERG	human ether-a-go-go-related gene
HNSTD	Highest non-severely toxic dose
HPLC	High performance liquid chromatography
HUVEC	human umbilical vein endothelial cell
IC50	concentration that results in 50% inhibition
IC90	concentration that results in 90% inhibition
ICH	International Conference on Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IgH	immunoglobulin H
IPC	In-process control test
IR	Infra-red
IV	intravenous
JAK	Janus kinase
JP	Japanese Pharmacopoeia
KF	Karl Fischer
LDH	Lactate dehydrogenase
LDPE	Low density polyethylene
LoA	Letter of Access
LoD	Limit of detection
LOD	Loss on Drying
LoQ	Limit of Quantitation
LRS	Lactated Ringer's solution
LSC	liquid scintillation counting
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MAPK	mitogen-activated protein kinase
MDD	Maximum Daily Dose
MRM	multiple reaction monitoring
mRNA	messenger ribonucleic acid
MS	Mass spectroscopy
MTBE	methyl t-butyl ether
MTD	Maximum tolerated dose
NC	Not calculated
NF	National formulary
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
OAT	organic anion transporter
OATP1	organic anion-transporting polypeptide 1
OCT2	organic cation transporter 2
OECD	Organisation for Economic Co-operation and Development
ORR	Objective response rate
PAR	Proven acceptable range
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic
PDA	Photo diode array
PDE	Permitted Daily Exposure
pFGFR	phosphorylated fibroblast growth factor
P-gp	p-glycoprotein

Ph.Eur.	European Pharmacopoeia
PK	pharmacokinetic
PO	orally
PR	Partial response
PVC	Polyvinyl chloride
PVdC	Polyvinyl dichloride
QC	Quality control
QD	once daily
QL	Quantitation limit
QOS	Quality Overall Summary
QTPP	Quality target product profile
QWBA	quantitative whole-body autoradiography
RBC	Red blood cell
RH	Relative Humidity
RMS	Reference member state
RP2D	recommended Part 2 doses
RRt	Relative retention time
Rt	Retention time
RT	Room temperature
SAL	Sterility assurance level
SBE-CD	sulphobutyl ether β-cyclodextrin
SC	subcutaneously
SD	standard deviation
SDH	Sorbitol dehydrogenase
SEM	standard error of the mean
SEM	Scanning electron microscopy
SmPC	Summary of product characteristics
STAT	signal transducer and activator of transcription
STD	Severely toxic dose
STD10	Severely toxic dose in 10% of the animals
t1/2	Time for plasma concentration to reduce by 50%
TA	Test article
TACC3	transforming acidic coiled-coil–containing protein 3
TGA	Thermo-Gravimetric Analysis
TLC	Thin layer chromatography
Tmax	Time of maximum observed plasma concentration
UGTs	UDP-glucuronosyltransferases
USP	United States Pharmacopoeia
UV	Ultra violet
UVR	ultraviolet radiation
VEGF	Vascular endothelia
VEGFR	vascular endothelial growth factor receptor
XRD	X-Ray Diffraction
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Incyte Biosciences Distribution B.V. submitted on 21 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Pemazyre, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 December 2018.

Pemazyre, was designated as an orphan medicinal product EU/3/18/2066 on 24 August 2018 in the following condition: treatment of biliary tract cancer.

The applicant applied for the following indication: Pemazyre is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.

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

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-002370-PIP01-18on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

Accelerated assessment

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

New active Substance status

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

Protocol assistance

The applicant received Scientific Advice/Protocol Assistance on the development relevant for the approved indication:

Date	Reference	SAWP co-ordinators
26 July 2018	EMEA/H/SA/3883/1/2018/I	Ms Audrey Sultana, Dr Sheila Killalea
31 January 2019	EMEA/H/SA/3883/2/2018/PA/III	Dr Alexandre Moreau, Dr Martin Mengel
19 September 2019	EMEA/H/SA/3883/2/FU/1/2019/PA/III	Dr Joao Manuel Lopes de Oliveira, Dr Sheila Killalea
17 October 2019	EMEA/H/SA/3883/3/2019/PA/III	Prof. Flora Musuamba Tshinanu, Dr Serena Marchetti

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

- The overall quality development strategy, including definition of starting materials and the bridging strategy to support development of additional tablet strengths.
- The overall non-clinical safety programme to support MAA in the approved indication.
- The design of an open-label, non-randomised study INCB 54828-202, and its potential to provide pivotal data to support an application for CMA.
- The design of a Phase 3, open-label, randomised, active-controlled study of pemigatinib in first-line treatment cholangiocarcinoma, and its adequacy to provide comprehensive data to convert a potential CMA to full MA.
- The adequacy of the overall clinical pharmacology plan to support MAA.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Janet Koenig

The application was received by the EMA on	21 November 2019
The procedure started on	2 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	26 March 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	1 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 April 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 April 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	4 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 September 2020
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	17 September 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	30 November 2020
SAG oncology was convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	3 December 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	8 December 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued by majority a positive opinion for granting a marketing authorisation to Pemazyre on	28 January 2021
A revised opinion was adopted by the CHMP in order to revise the indication upon late comment raised on inadequacy of use of relapse and refractory in the frame of a solid tumour indication, on	25 February 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

2.1.2. Epidemiology and risk factors

Cholangiocarcinomas account for approximately 3% of all gastrointestinal cancers and approximately 10% of primary liver cancers (Bergquist and von Seth 2015, Khan et al 2019, Tyson and El-Serag 2011), with a prevalence in autopsy studies of 0.01 to 0.46 percent.

The incidence of cholangiocarcinoma is rare, with 1 to 2 patients per 100,000 in regions like the United States and the United Kingdom. However, liver fluke and other parasitic infections give rise to a much higher incidence in Southeast Asia (113 per 100,000 person-years in men and 50 per 100,000 person-years in women; Bergquist and von Seth 2015). Recent epidemiological studies have shown that incidences of intrahepatic cholangiocarcinoma and associated mortality are increasing, while the incidence of extrahepatic cholangiocarcinoma appears to be stable or decreasing (Khan et al 2019, Verlingue et al 2017).

Cholangiocarcinoma (CCA) is a heterogeneous disease arising from a complex interaction between host-specific genetic background and multiple risk factors.

In the United States and Europe, the main risk factors are primary sclerosing cholangitis (PSC) and fibropolycystic liver disease (e.g., choledochal cysts). There is a clear and strong association between chronic intrahepatic stone disease (hepatolithiasis, also called recurrent pyogenic cholangitis) and cholangiocarcinoma. Chronic liver disease (cirrhosis and viral infection) is now recognised as a risk factor, particularly for intrahepatic cholangiocarcinoma. Finally, at least four genetic conditions, Lynch syndrome, BRCA-associated protein-1 (BAP1) tumour predisposition syndrome, cystic fibrosis, and biliary papillomatosis, appear to increase the risk for cholangiocarcinoma. Moreover, despite the advancements in the knowledge of CCA aetiology, in Western countries about 50% of cases are still diagnosed without any identifiable risk

factor. It is therefore conceivable that other still undefined etiologic factors are responsible for the recent increase of CCA (especially iCCA) incidence worldwide. (Khan et al, 2019)

FGFR genetic aberrations (GAs) occur in an estimated 10% to 16% of intrahepatic cholangiocarcinomas (CCAs). The natural history of CCA with FGFR GAs, the prognostic role of coexisting GAs, and the outcome with FGFR-targeted inhibitors are still under discussion. The frequency of FGFR2 alterations in cholangiocarcinoma patients is reported to be between 9% and 14.3%, with a weighted average of 11.2%. These alterations have been interchangeably referred to as translocations, fusions, or rearrangements. Breakpoint is within the FGFR2 intron 17/exon 18 hotspot and different partner genes. Patients with FGFR2 rearrangement or fusion are reported to have a better prognosis than patients without FGFR genetic alteration (Churi et al, 2014; Jain et al, 2018).

2.1.3. Biologic features, aetiology and pathogenesis

Cholangiocarcinoma is a malignant growth originating in the epithelial lining of the biliary tree and it is commonly classified based on anatomical location; extrahepatic cholangiocarcinoma, which includes hilar and distal tumours, accounts for the majority of cases, while intrahepatic cholangiocarcinoma accounts for less than 10% of cases (DeOliveira et al 2007, Nakeeb et al 1996).

The level of understanding of the molecular pathogenesis of cholangiocarcinoma is significantly less than that of other gastrointestinal cancers. Molecularly, the precursors of carcinoma remain poorly characterised.

With emerging technologies, including next-generation sequencing (NGS), actionable mutations in the isocitrate dehydrogenase (IDH1/2), FGFR2, BRAF, and HER2/neu genes have been identified for targeted therapeutics in CCA and gallbladder cancer.

The fibroblast growth factor receptor (FGFR) family consists of four transmembrane receptors (FGFR1 to FGFR4), 18 FGF ligands, and a heparan sulfate proteoglycan that stabilises and sequesters the FGFs. The ligand-receptor combination is responsible for the activation of downstream RAS/RAF/MEK, JAK/STAT, and PI3K/AKT pathways. Genetic aberrations (GAs) such as activating mutations, amplifications, or chromosomal translocations/fusions in the FGFR pathway contribute to malignant transformation.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The prognosis for cholangiocarcinoma is generally poor owing to the aggressive nature of the disease, the paucity of effective treatment options, and the late stage at which the disease is typically diagnosed. The 5-year survival rate by American Joint Committee on Cancer stage is 50% for Stage I, 30% for Stage II, 10% for Stage III, and 0% for Stage IV (Valle et al 2017). The majority of patients with cholangiocarcinoma (> 65%) have nonresectable disease at the time of diagnosis, and the rate of recurrence is high among patients in the minority who are able to undergo potentially curative surgery.

The natural history of CCA with FGFR alterations and its prognostic role is not fully characterised. Retrospective studies have shown that FGFR alterations (predominantly FGFR2 fusions), contrary to the general CCA population, occur more frequently in younger women and seem to confer better prognosis (Graham et al 2014, Churi et al 2014).

2.1.5. Management

Cholangiocarcinoma is a lethal disease for which there is significant unmet need for new therapies. No agents are approved in the second-line setting. For most patients, palliative chemotherapy is the only treatment option. The first-line, standard-of-care treatment for patients with unresectable and metastatic disease is gemcitabine and cisplatin (ESMO 2016).

There is no established systemic therapy once cholangiocarcinoma has progressed on first-line therapy. Likewise, locoregional therapies, including transarterial chemoembolisation, hepatic arterial infusion, percutaneous ablation, external beam radiation therapy, and radioembolisation (Koay 2017), are not recommended for routine use due to a lack of prospective data (Labib et al 2017). Per ESMO and NCCN guidelines, clinical trials are recommended in the second line and above settings as the next treatment option. According to clinical data collected in a database of the Hannover Medical School (Germany), patients received different chemotherapy regimens in second- and third-line treatment (e.g. FOLFOX and FOLFIRI).

About the product

The mammalian fibroblast growth factor receptor family (FGFR1, FGFR2, FGFR3, and FGFR4) have an extracellular ligand binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain (*Dailey et al, 2005*). Eighteen fibroblast growth factor (FGF) ligands, divided into canonical and hormonal FGFs, bind to FGFRs leading to receptor dimerisation, activation of the kinase domain, and transphosphorylation of the receptors. Signalling through the FGF-FGFR pathway happens e.g. via activation of downstream RAS/RAF/MEK, JAK/STAT and PI3K/AKT pathways and is controlled through feedback regulation. In many cases, FGFR pathway activation promotes cell proliferation, survival, and migration; however, cellular context plays an important role, and in certain tissues, FGFR signalling results in growth arrest and cellular differentiation.

FGFRs have multiple phosphorylation sites for activation of the protein. FGFR2 can be phosphorylated at tyrosine residues Y466, Y586/588, Y733, Y724, Y719, and Y653/654; phosphorylation at Y653/654 is a key phosphorylation site and is autophosphorylated in FGFR2-amplified cells. FGFR2 Y653/654 phosphorylation has been shown to cause downstream activation of the PLCγ, MAPK, JAK/STAT, and PI3K signalling pathways. Phosphorylation of the tyrosine kinase domain in FGFRs is required for FGFR signalling pathway activation. This is the rationale provided for using the cellular levels of pFGFRs as a pharmacodynamic (PD) marker to monitor FGFR activation and inhibition in clinical development of a FGFR inhibitor.

Pemigatinib is a small molecule, with a molecular weight of 487.5 Da and is classified as a class 2 compound in the Biopharmaceutical Classification System (BCS) due to its limited in vitro solubility at neutral pH and high permeability. Indeed, pemigatinib show a pH-dependent aqueous solubility, with higher pH resulting in lower solubility (< 0.001 mg/mL at pH 7.4) and high in vitro permeability in Caco-2 cells (11 × 10-6 cm/sec).

Pemigatinib is a small molecule tyrosine kinase inhibitor of FGFR1, FGFR2, and FGFR3. Pemazyre inhibits FGFR phosphorylation and signalling and decreases cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements. These genetic alterations in FGFR genes result in activation of FGFR signalling that supports the proliferation and survival of malignant cells. Cancer cell lines that have activating molecular alterations in FGFR1, FGFR2, and FGFR3 are

more sensitive to growth inhibition by pemigatinib, with IC50 values mostly in the range of 3 to 50 nM, than cancer cell lines or normal cells without FGFR dependence (IC50 > 1500 nM).

Genomic characterisation of cholangiocarcinoma has identified potentially actionable molecular alterations that may drive tumorigenesis, including alterations in genes encoding FGFRs, which regulate cell proliferation, survival, migration, and angiogenesis. Comprehensive genomic profiling has identified FGFR2 fusions in approximately 9% to 14% of cholangiocarcinoma patients (Javle et al 2019, Lowery et al 2018).

FGFR2 rearrangements are generated by interchromosomal translocations and intrachromosomal inversions, duplications, or deletions. DNA-based next generation sequencing assays provide resolution on the molecular details of genomic rearrangements, which include the following FGFR2 rearrangement classifications:

- An FGFR2 rearrangement predicted to be a fusion: Breakpoint is within the FGFR2 intron 17/exon 18 hotspot and the partner gene is known in the literature or is a novel partner that is predicted to be in-frame with FGFR2.
- An FGFR2 rearrangement, which cannot be confidently predicted to be a fusion: Breakpoint is within the FGFR2 intron 17/exon 18 hotspot, but the partner gene is novel and out-of-frame or out-of-strand with exon 17 of FGFR2. Alternatively, the downstream end of the breakpoint may be in an intergenic region and not within another gene (designated as partner N/A).

The common findings in these rearrangements are 1) that the genomic breakpoints occur in the intron 17/exon 18 hotspot, downstream of the last kinase domain-encoding exon, with the kinase domain remaining intact, and 2) that the FGFR2 rearrangements and fusions lack C-terminal residues, leading to ligand-independent activation, decreased receptor internalisation/degradation, increased receptor autophosphorylation/activation, and sustained activation of FRS2 (Cha et al 2009, Itoh et al 1994, Javle et al 2019, Lorenzi et al 1997). These similarities predict that pemigatinib's FGFR inhibitory activity will be similar across patients with cholangiocarcinoma with FGFR2 rearrangements classified either as fusions or as rearrangements.

Pemigatinib is under development for the treatment of malignant diseases or other diseases related to FGFR dysregulation. In the current submission, the applicant seeks marketing approval for pemigatinib as monotherapy for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy. The proposed recommended dose of Pemazyre is 13.5 mg taken orally once daily for 14 days followed by 7 days off therapy. The drug product for registration is an immediate release tablet proposed at three strengths 4.5, 9 and 13.5 mg.

Type of Application and aspects on development

The CHMP did not agree to the applicant’s request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that:

- Available data seemed to indicate that FGFR2 tumours could be associated with a relatively indolent disease course, reflecting a distinct clinical phenotype with a better prognosis in the target indication.
- Data presented at the time of the request did not allow to conclude definitely that the medicinal product was likely to be of major public health interest from the point of view of public health, and the CHMP were of the opinion that the presented efficacy data did not justify *per se* an accelerated assessment. (CHMP conclusion on 19/09/2019).

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. In addition to the submission of the final study report for study INCB 54828-202, submission of the data from a comparative confirmatory study INCB 54828-302 is proposed to provide additional evidence and further quantify the positive benefit-to-risk ratio of pemigatinib in patients with cholangiocarcinoma with FGFR2 fusion or rearrangement.
- Unmet medical needs will be addressed, as pemigatinib has demonstrated meaningful and durable antitumour activity and an acceptable safety profile in patients with FGFR2-rearranged cholangiocarcinoma relapsed or refractory to at least one line of systemic therapy for whom there are no approved treatment options.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. In view of the favourable benefit-risk profile and the unmet medical need in the targeted patient population for whom there is currently no effective approved therapy, the immediate availability of pemigatinib for these patients clearly outweighs the risk inherent to the fact that comparative data to further quantify the clinical benefit is needed.

The clinical development programme of pemigatinib in previously treated locally advanced/metastatic or surgically unresctable cholangiocarcinoma with a FGFR2 fusion or rearrangement consists of three clinical studies:

- Two Phase I open-label, multicentre, dose escalation and expansion studies (Study INCB 54828-101 in participants with advanced malignancies and study INCB 54828-102 in Japanese participants with advanced solid tumours)
- One Phase II open-label, single-Arm, multicentre study (Study INCB 54828-202 in participants with advanced/metastatic or surgically unresectable cholangiocarcinoma including FGFR2 translocations who failed previous therapy).

Scientific advices in July 2018 (EMEA/H/SA/3883/1/2018/I), in January 2019 (EMEA/H/SA/3883/2/2018/PA/III), and follow-up scientific advices in September 2019 (EMEA/H/SA/3883/2/FU/1/2019/PA/III) and in October 2019 (EMEA/H/SA/3883/3/2019/PA/III) were provided by the Committee on Human Medicinal Products (CHMP).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 4.5, 9 or 13.5 mg of pemigatinib as active substance.

Other ingredients are microcrystalline cellulose (E-460), sodium starch glycolate (Type A) and magnesium stearate (E-572).

The product is available in PVC/Al blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of pemigatinib is 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2*H*-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one corresponding to the molecular formula $C_{24}H_{27}F_2N_5O_4$. It has a relative molecular mass of 487.5 g/mol and the following structure:

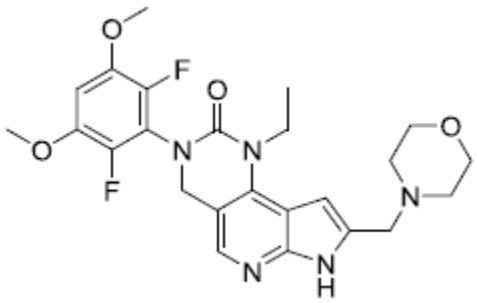


***Figure 1*: active substance structure**

The chemical structure of pemigatinib was inferred from the route of synthesis and elucidated by a combination of Fourier Transform Infrared spectroscopy (FT-IR), ^{1}H, ^{13}C, and ^{19}F nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry, ultraviolet (UV) spectroscopy and elemental analysis. The solid-state properties of the active substance were measured by a combination of particle size analysis, polymorph screening (by X-ray powder diffractometry (XRPD), differential scanning calorimetry (DSC), and thermal gravimetric analysis (TGA), determination of melting/decomposition temperature, hygroscopicity analysis (by dynamic vapor sorption (DVS)) and assessment of the effect of humidity cycling on solid form (by XRPD analysis before and after the DVS experiment). Polymorph screening revealed multiple polymorphic forms, mostly solvates. Form I, the chosen commercial form, is the most thermodynamically stable, is routinely produced by the commercial manufacturing process and is confirmed by a test (XRPD) in the active substance release specification.

The active substance is a white to off-white non-hygroscopic crystalline solid. Solubility varies across the pH range from being highly soluble at acidic pH to slightly soluble at pH 7.4. It is soluble in simulated gastric fluid but less so in simulated intestinal fluids (solubility is higher in FeSSIF than FaSSIF).

Pemigatinib is achiral.

Manufacture, characterisation and process controls

Pemigatinib is synthesised in five main steps using well defined starting materials with acceptable specifications. The choice of starting materials was adequately justified in line with ICH Q11.

Adequate in-process controls are applied during the synthesis. The control of process parameters and input material attributes for each step have been adequately justified. The specifications and control methods for intermediate products, starting materials and reagents have been presented. An extensive discussion on potential impurities and their control in the active substance manufacturing process was presented including

fate and purge studies, discussion of impurities in starting materials and intermediates, related substances, residual solvents, elemental impurities and genotoxic impurities.

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

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Two synthetic processes, Process A and Process B were developed and used to produce batches pemigatinib. The routes use different starting materials, reagents and intermediates. Process A was used to produce active substance used in early development such as animal toxicology studies and early clinical studies. Process B is more efficient and has therefore been selected as the commercial manufacturing process for future production of pemigatinib. Changes introduced have been presented in sufficient detail and have been justified. Process B produces active substance of suitable quality. Particle size distribution and polymorphic form are controlled by the final recrystallisation step.

The active substance is packaged in LDPE endless liner placed in HDPE container which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification, shown in, includes tests for description (visual inspection), identity (FT-IR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (Ph. Eur.), elemental impurities (ICP-MS), crystallinity (XRPD) and particle size distribution (laser diffraction).

Limits for impurities are set according to ICH Q3A. The array of tests is deemed adequate to ensure the quality of the active substance. The omission of a test for microbiological quality has been justified.

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

Batch analysis data nine production scale batches of the active substance manufactured by the proposed commercial process B were provided. Additional data from three batches manufactured with process A were also provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from six pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Samples were tested for description, related substances, assay, water content, crystallinity and particle size. The analytical methods used were the same as for release. No significant changes were observed to any of the measured parameters and no trends were seen.

Photostability testing following the ICH guideline Q1B was performed on one batch demonstrating the pemigatinib is not photosensitive.

Forced degradation studies under stressed conditions (acid, base or oxidant in aqueous solution) indicate the pemigatinib exhibits excellent stability. This study also demonstrated that the analytical methods are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period and storage conditions.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Pemigatinib finished product is supplied as immediate-release uncoated tablets for oral administration in strengths of 4.5 mg, 9 mg and 13.5 mg. A brief description of each strength tablet is provided below:

4.5 mg tablet: round shaped (5.8 mm diameter) white to off-white tablet, debossed with "I" on one side and with "4.5" on the other side;

9 mg tablet: oval shaped (10 mm by 5 mm) white to off-white tablet, debossed with "I" on one side and with "9" on the other side;

13.5 mg tablet: round shaped (8.5 mm diameter) white to off-white tablet, debossed with "I" on one side and with "13.5" on the other side.

The aim of development was to identify an immediate-release orally available dosage form containing the requisite amount of pemigatinib. Initially, 0.5 and 2 mg tablets were developed but the clinical programme revealed that 3 tablet strengths were needed for routine use: 4.5, 9 and 13.5 mg. A formulation was developed which is qualitatively and quantitatively proportional across the three proposed commercial dosage strengths. Bridging between formulations and strengths was achieved by way of clinical bioequivalence studies during development.

The free base form of the active substance was found to be optimum for development, being freely soluble at acidic pH, non-hygroscopic, stable and compatible with the excipients in the commercial formulation. Pemigatinib free base is a BCS class 2 molecule, though exhibits BCS class 1 properties in acidic media such as the stomach. The manufacturing process of the active substance routinely produces active substance with the thermodynamically stable polymorphic form and a small particle size which aids content uniformity and dissolution. Although other polymorphs were observed during development, it has been shown that the desired form is conserved under stressed conditions and during formulation.

Based on this, the applicant developed a quality target product profile (QTPP) which is summarised in Table 1.

Table 1: Pemazyre QTPP

Product Attribute	Development Target	Outcome for Pemigatinib Tablets, 4.5 mg, 9 mg, and 13.5 mg
Route of administration	Oral	Oral
Dose range and Frequency	As required according to clinical trials	Max dose 13.5 mg/once daily
Dosage Form	Immediate release solid oral dosage form	Immediate release tablet, dose-weight proportional for the three strengths
Pharmacokinetics	Orally bioavailable with maximum plasma concentrations achieved within hours after dosing of an immediate release drug product formulation	Complies with target

Product Attribute	Development Target	Outcome for Pemigatinib Tablets, 4.5 mg, 9 mg, and 13.5 mg
Product shelf-life and storage conditions	Minimum 36 months at room temperature. Degradation products below ICH qualification thresholds throughout shelf life	36 months stored in blister cards at room temperature at time of marketing application submission. Degradation profile as targeted.
Requirement to assure safety and efficacy at release and during shelf-life	All appropriate quality criteria are met (for appearance, identification, assay, content uniformity, dissolution, impurities, water content, and microbial content).	Complies with target
Subjective properties	Uniform in color, product differentiation	Complies with target
Manufacturing process	Robust and reproducible, utilizing standard manufacturing equipment	Complies with target
Container Closure System	Blister packaging sufficiently protective to assure the product quality throughout its shelf life.	Complies with target

Accordingly, a simple formulation was developed containing three commonly used excipients – a filler, a disintegrant and a lubricant. The relative levels of individual excipients were optimised through multivariate studies to arrive at the final commercial formulation. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

At day 120, CHMP raised a multifaceted major objection in relation to the development of the dissolution method, investigation of its discriminatory power, and the proposed specification. The applicant provided

additional data on dissolution profiles of tablets made with more meaningful changes in composition and process parameters and agreed to tighten the dissolution specification. Despite the additional studies, discriminatory power of the selected QC method could not be shown, which was considered acceptable since the finished product dissolves rapidly in the most feasible dissolution medium. Accordingly, batch to batch consistency is more appropriately controlled by disintegration testing which is conducted as an IPC during tabletting.

Detailed information on manufacturing process development was provided. The manufacturing process is identical for all tablet strengths and uses conventional pharmaceutical processes: blending and tableting. Design of Experiments (DoE) were performed on each of the unit operations (blending, lubrication, compression) to investigate the impact of varying process parameters on the finished product's critical quality attributes (CQAs, defined as assay, content uniformity and dissolution). These studies allowed exploration of the robustness of the process and the setting of appropriate set-points and proven acceptable ranges (PARs) for process parameters. These studies allowed the control strategy to be defined which consists of the following elements in line with ICH Q8:

- Control of excipients for tablet manufacture in accordance with compendial standards;
- Control of active substance solid-state form and particle size;
- In-process controls that have been identified and refined during the development process to produce a finished product of the desired quality;
- Set-points and PARs for process parameters;
- The finished product specification which provides the final control and assurance that the tablets meet their intended critical quality attributes.

The primary packaging is a PVC/Al blister. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of three main steps: milling and blending, lubrication and compression. The process is considered to be a standard manufacturing process.

Since the process is considered standard, formal process validation does not need to be submitted in the dossier. Validation data was provided on pilot scale on the critical lubrication and compression steps. The process will be validated on production scale prior to commercialisation and an acceptable validation protocol has been submitted in that regard. In addition, the applicant plans to conduct continued process validation throughout lifecycle to ensure that the process remains in a state of control. Studies conducted so far indicate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual inspection), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), water content (Ph. Eur.), content uniformity (Ph. Eur.), dissolution (Ph. Eur.) and microbial limits (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. All potential sources (active substance, excipients, manufacturing equipment train and container/closure system) were considered. Batch analysis data from 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE and justifying that routine testing is not required.

A risk evaluation concerning the potential presence of nitrosamine impurities in the finished product was submitted considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, no risk was identified and no additional control measures are deemed necessary.

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

Batch analysis results are provided for one lab scale and two pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Supportive batch data from historical batches used throughout the clinical programme were also provided and all results were within specification.

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

Stability of the product

Stability data from one lab scale batch and two pilot scale batches of finished product of each strength for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing (other than having fewer tablets per blister pack). Samples were tested for description, assay, degradation products, water content, dissolution and microbial limits. The analytical procedures used are stability indicating as shown by forced degradation studies. No significant changes to any of the measured parameters were observed other than an increase in water content (within specification), as a result of which, extrapolation of shelf-life beyond 6 months of the completed long-term studies is not possible.

At the request of CHMP, the applicant added the tablet dimensions to the release and shelf-life specification. These are quite wide and may be due to the observed uptake of water over time. As a result, the applicant is

requested to measure the dimensions and hardness of the tablets at shelf-life. The applicant committed to measuring these properties at the next timepoint of the on-going stability study.

One batch of 9 mg tablets was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No degradation was observed indicating that the finished product is photostable.

A freeze-thaw study was conducted on 4.5 mg and 13.5 mg tablets via four cycles alternating daily between -20ºC and 25ºC / 60% RH. No significant changes occurred in appearance, assay, related substances, water content, and dissolution.

Based on available stability data, the proposed shelf-life of 30 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is off vegetable origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The major objection on development and discriminatory power of the dissolution method was adequately addressed by provision of dissolution data on additional batches with meaningful differences in manufacturing parameters and by tightening the release specification. Additional data on tablet dimensions and hardness will be gathered at the next timepoint of the stability study and has been added to the specification accordingly.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation for future quality development

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

- the applicant should provide data of tablet dimensions and hardness at shelf-life to justify the wide range of tablet dimensions in the finished product specification.

2.3. Non-clinical aspects

2.3.1. Introduction

Overall the studies were performed in compliance with the OCDE GLP except for the phototoxicity study where a formulation analysis was not performed. Twelve non-clinical GLP safety studies were completed between September 2014 and January 2017 at U.S. facilities and trial sites.

2.3.2. Pharmacology

The nonclinical testing strategy to characterise the pharmacodynamic effects of pemigatinib included *in vitro* and *in vivo* non-GLP studies and a series of GLP safety pharmacology studies. *In vitro* studies included enzyme-based assays measuring inhibition of FGFR1, FGFR2, FGFR3 and related enzymes as well as cell-based assays to measure the effects of FGFR inhibition on FGFR-dependent signalling and proliferation. *In vivo*, pemigatinib was evaluated in a number of xenograft tumour models including FGFR1-fusion positive AML, cholangiocarcinoma, and bladder cancer that are dependent upon FGFR1, FGFR2, and FGFR3 activity, respectively. Pemigatinib was also tested in naïve mice for pharmacodynamic effects on phosphate. Pemigatinib was evaluated in non-GLP studies to assess its selectivity in a panel of binding and kinase profiling assays. GLP safety pharmacology studies included an assessment of the respiratory and central nervous system effects of pemigatinib in rats, cardiovascular effects in conscious telemetered cynomolgus monkeys, and determination of the hERG IC50. Safety pharmacology studies were conducted in accord with ICH guidelines S7A and S7B.

Primary pharmacodynamic studies

The applicant has conducted numerous nonclinical studies that characterise the pharmacodynamics properties of pemigatinib.

In an enzymatic assay, pemigatinib inhibited the tyrosine kinase activity of FGFR1-4 with an IC50 of 0.39, 0.46, 1.2 and 30 nM, respectively. The binding affinity of pemigatinib was tested in a panel of 192 kinases (PerkinElmer); pemigatinib inhibited all 4 members of the FGFR family by 99%, 99%, 98%, and 77%; other kinases were inhibited with less affinity. The kinase profile of pemigatinib was further evaluated with 56 non-FGFR kinases (in-house kinase assay); the results from this assay indicated the selectivity of pemigatinib against the FGFR family as demonstrated by an ≥ 467 fold (FGFR1), ≥ 396 fold (FGFR2), and ≥ 152 fold (FGFR3) increase in the IC50 values for the 56 non-FGFR family kinases. The inhibitory potency of pemigatinib was also evaluated against VEGFR2 considering that this non-FGFR kinase was most potently inhibited by pemigatinib. Two different studies showed that the IC50 for VEGFR2 was 71 ± 10 nM (at 1 mM ATP), in a screening assay using an unphosphorylated form of VEGFR2 (n=8) and 182 nM. A cellular growth assay using human umbilical vein endothelial cells showed greater than 80-fold difference in the potency of INCB054828 to inhibit FGF-dependent growth compared with VEGF-dependent growth with an estimated IC50 of 800 nM. No dedicated *in vivo* studies were completed to test this activity.

Pemigatinib inhibited growth of KATOIII cells expressing FGFR2 (IC50 22.6 nM); antiproliferative activity of pemigatinib was shown in selected cancer cell lines from various tissues, including cholangiocarcinoma cells with FGFR2 translocation, bladder cancer cells with FGFR3 translocation and human AML cells with FGFROP2-

FGFR1 translocation. In a human whole blood assay, pemigatinib blocked phosphorylation of FGFR2 with an IC50 of about 11 nM.

Pemigatinib inhibited autophosphorylation of FGFR proteins in cancer cell lines displaying activated FGFR1, 2 and 3 and phosphorylation of key downstream signalling components of the FGFR signalling pathways in KG-1A cells (i.e. ERK1/2, and STAT5).

Similarly, pemigatinib demonstrated anti-proliferative activity (IC50) in cell lines that have genetic amplification of FGFR1 (H1581, DMS114) and FGFR2 (KATOIII), FGFR2 mutation (AN3CA) or harbour chromosomal translocations involving FGFR1 (KG-1A) or FGFR3 (RT-112). In addition, inhibition of cancer cell growth could also be demonstrated in Ba/F3 cells expressing the 8p11 myeloproliferative neoplasm fusion FGFR1-ZFN298 or cholangiocarcinoma fusions FGFR2-CCDC6 and FGFR2-AHCYL (IC50 0.9, 1.2, and 1.1, respectively). In summary, the in vitro data demonstrated inhibitory effects of pemigatinib against FGFR1, FGFR2, and FGFR3 with similar impacts against FGFR1 and FGFR2 and, is thus in line with other known pan-FGFR inhibitors like AZD4547 and Ly2874455.

In vivo, pemigatinib demonstrated antitumour activity in rodents bearing tumours derived from multiple human cancer cell lines with FGFR1, 2, and 3 alterations (translocation or amplification) including gastric, cholangiocarcinoma, bladder, and in a mouse study using patient-derived xenografts originated from blood expressing FGFR1 fusion protein. Significant tumour inhibition was dose- and time-dependent. Maximal efficacy was achieved when the IC50 was covered for at least 8 hours (gastric cancer) to 17 hours (bladder cancer model). At the projected efficacious clinical dose of 6 mg QD, plasma concentrations are anticipated to exceed the whole blood IC50 value for the dosing interval. Further, one of the endogenous biomarkers of FGFR inhibition is phosphate induction through inhibition of FGF23 signalling in the kidney. Following administration of one single dose of pemigatinib in mice an increase of phosphate in a dose-dependent manner was shown emphasizing the essential role of FGFR signal transduction in phosphate homeostasis**.**

Overall, the in vitro and *in vivo* data provided underline the potency of pemigatinib in the treatment of FGFR-dependent cancers.

Pemigatinib is considered to be a competitive inhibitor of ATP.

Secondary pharmacodynamic studies

No significant cross reactivity defined as more than 50% inhibition has been observed on 70 receptors, ion channels, transporters, and enzymes. INCB054828 inhibited FGFR1, FGFR2, FGFR3, and FGFR4 by 99%, 99%, 98% and 77%, respectively. The compound showed an inhibition in the range of 20% to 49% for the following targets: Histamine H3, Serotonin 5HT1A (h), Sodium Site 2, Neurokin NKI, thromboxane A2. Clinical relevance of the effect of pemigatinib on these targets in comparison with the therapeutic doses of 13.5 mg was 0.025 µM, which is 40-fold lower than the concentration where marginal activity was noted. Based on the substantial safety margin, these findings were not considered to be clinically relevant.

Table 2

Study type / study number	Test system/ method	Noteworthy findings

Receptor Binding Profile **T13-05-07**	• PerkinElmer Customised Screening Programme • 70 receptors, ion channels, transporters, and enzymes • *In vitro* 0.1 and 1.0 µM	• No significant cross reactivity, defined as > 50% inhibition. • *Compounds which show inhibition in the range of 20% to 49%:* Histamine H3, Serotonin 5HT1A (h), Sodium Site 2, Neurokin NKI, Thromboxane A2
Kinase Selectivity Profile **ATG-14.03.1**	• 56 kinase assay • *In vitro* 0.1 µM	• INCB054828 exhibited ≥ 151-fold selectivity against 56 non-FGFR kinases evaluated in this study. • KDR and KIT showed IC50 < 300 µM • INCB054828 is selective towards the target enzyme Fibroblast growth factor receptor (FGFR), as demonstrated by ≥ 467-fold (FGFR1), ≥ 396-fold (FGFR2), and ≥ 152-fold (FGFR3) increase in IC50 value for the 56 non-FGFR family kinases evaluated in this study.
Kinase Selectivity Profile **T13-05-06**	• 192 kinase assays • *In vitro* 0.1 µM	• INCB054828 inhibited FGFR1, FGFR2, FGFR3, and FGFR4 by 99%, 99%, 98% and 77%, respectively. No significant inhibition < 50%) of other kinases was observed at 100 nM. • KDR and FLT4 show inhibition of approximately 45%

Safety pharmacology programme

Standalone studies on cardiovascular, respiratory and central nervous systems were performed.
The effects of pemigatinib were tested on the potassium hERG currents and showed statistically significant inhibition of hERG channel currents from 3µM (IC_{50} estimated > 8 µM). Pemigatinib was also evaluated in an *in vitro* GLP hERG channel assay. The IC50 for hERG inhibition was > 8µM (the highest feasible concentration based on solubility), that is > 360-fold higher than the clinical steady-state unbound Cmax at the dose of 13.5 mg.

In Vitro cardiovascular Safety Pharmacology

Table 3

Study type / study number / GLP	Test system/ method	Noteworthy findings
Effect of Pemigatinib on Cloned hERG Channels Expressed in Mammalian Cells	• HEK293 cells transfected with hERG cDNA • Incubation • 3 and 8 µM	• INCB054828 inhibited hERG current by 5.8 ± 0.3% (Mean ± SEM) at 3 µM and 14.1% ± 0.2% at 8 µM. The IC_{50} was > 8 µM. • Mean human steady-state Cmax (22.2 nM unbound) at the clinical dose of 13.5 mg QD in humans is > 360-fold lower than 8 µM (the highest concentration tested, which resulted in 14.1% hERG inhibition). • Pemigatinib is not expected to cause any effect on ventricular repolarization via hERG inhibition.

T14-04-09 **GLP**		

In Vivo Safety Pharmacology on Cardiovascular, Respiratory and SNC Systems

Table 4

Study type / study number /	Test system/ method	Noteworthy findings
Effects of Pemigatinib on the Central Nervous System in the Rat **T16-02-05** **GLP**	• Sprague-Dawley rats • 6/sex/group • single oral dose • 0, 0.5, 1.5, or 10 mg/kg • Irwin test • 60, 120, 240, and 360 min postdose	• Piloerection in a single 10 mg/kg male and increased touch response in a single 10 mg/kg male and female were considered potentially pemigatinib-related, but not adverse. • Cmax and AUC values increased with dose in a greater than dose proportional manner. • Plasma exposures were greater in females compared to that in males. • Terminal half-life values increased with dose in males, independent of dose in females. **Conclusions:** The NOAEL for central nervous system effects following a single oral administration of pemigatinib was 10 mg/kg, the highest level tested on study.

Effects of Pemigatinib on the Respiratory System in the Rat **T16-02-06** **GLP**	• Sprague-Dawley rats • 8/sex/group • single oral dose • 0, 0.5, 1.5, or 10 mg/kg • plethysmography chambers • Captured for 60min predose and continuously for 6h postdose.	• Lower respiratory frequency (1.5 and 10 mg/kg) during the initial 0-15 minute postdose period, higher (14.6%) respiratory frequency (10 mg/kg) for the individual subphase from 316-330 minutes postdose. • These changes, although pemigatinib-related, were not considered adverse based on their relatively small magnitude and short duration of the effects. • The integrated respiratory parameter minute volume was not affected. **Conclusions**: The NOAEL for respiratory function following a single oral (gavage) administration of pemigatinib was 10 mg/kg, the highest level tested on study.

Effects of Pemigatinib on the Cardiovascular System in Conscious Radiotelemetry-Implanted Cynomolgus Monkeys **T16-02-07** **GLP**	• single oral dose • 0, 0.33, 1, or 5 mg/kg • Male cynomolgus monkeys • radio telemetry-implanted • Each treatment once, with an approximately 7-day washout period between doses. • Collected continuously for approximately 1h prior to dosing through approximately 24h postdose.	• No significant changes in heart rate, systolic, diastolic, or mean arterial pressure, pulse pressure, body temperature, ECG interval duration (PR, QRS, RR, QT, or heart-rate corrected QT interval with the Bazett's correction formula [QTcB]), ECG waveform morphology, or the clinical condition of the animals. • Qualitative changes in ECG noted on the study (premature atrial conduction and premature ventricular contractions) were not considered to be the result of pemigatinib administration due to the sporadic nature of the findings, presence of findings in the same animals following administration of the vehicle, and the lack of any dose response relationship. Also, these findings can be common in monkeys of this species (Atterson et al 2009). • Plasma concentrations were consistent with corresponding values from the first day of dosing in the GLP 28-day study. **Conclusions:** The NOEL for cardiovascular effects of oral administration of pemigatinib to male radiotelemetry instrumented cynomolgus monkeys was 5.0 mg/kg, the highest dose tested**.**

Pharmacodynamic drug interactions

DDI assessment was adequate based on *in vitro* and clinical DDI studies. Therefore, there was no need to conduct *in vivo* nonclinical pharmacokinetic drug interactions studies.

2.3.3. Pharmacokinetics

Methods of analysis

Concentrations of pemigatinib in animal plasmas were determined by LC-MS/MS validated in rat and monkey plasmas over the range 1-1000 ng/ml for the 2 species. The full validation of measurement included selectivity, linearity, LLOQ, carry-over, intra-and inter-assay precision and accuracy, stock solution stability, short-term matrix stability, freeze-thaw and long-term matrix stability and dilution integrity. All the results

met the acceptance criteria. The method was suitable for the determination of pemigatinib in animals' plasmas within the defined stability limits in the range 1 to 1000 ng/ml. The validations of the bioanalysis methods applied in pivotal toxicity studies. No data were submitted concerning the Radiolabelled Bioanalytical Methods.

ADME

The absorption, distribution, metabolism, and excretion of pemigatinib were studied in Sprague Dawley rats, cynomolgus monkeys, and beagle dogs. Pemigatinib exhibited pH dependent aqueous solubility and high in vitro permeability. In single oral dose pharmacokinetic studies conducted in rats, dogs, and monkeys, pemigatinib was absorbed rapidly with Tmax values ranging from 0.56 and 2.0 hours. The oral bioavailability was moderate in monkeys (29%), and complete in rats and dogs. Following intravenous (IV) administration, the systemic clearance of pemigatinib was low in monkeys and dogs (8% and 10% of hepatic blood flow, respectively), but moderate in rats (31% of hepatic blood flow). Pemigatinib exhibits a low to moderate volume of distribution in all 3 species, ranging from 0.584 (monkey) to 3.49 (dog) L/kg. The terminal elimination half-life following IV dosing ranged from 4.0 hours (rat) to 15.7 hours (dog). The unbound renal clearance of pemigatinib exceeds the glomerular filtration rate in dogs and monkeys, suggesting active secretion. The % dose excreted as intact pemigatinib in urine was 9%, 36%, and 22% in rats, monkeys, and dogs, respectively.

After a single oral dose of 14C-pemigatinib, the drug-derived radioactivity was widely distributed to tissues in Sprague Dawley (nonpigmented) and Long-Evans (pigmented) rats. A comparison of tissue distribution results between nonpigmented and pigmented rats generally showed similar patterns of distribution and tissue concentrations, except for higher concentrations of radioactivity in pigmented tissues, suggesting an association of 14C-pemigatinib derived radioactivity with melanin. Pemigatinib has limited penetration across the blood brain barrier in rodents. The fraction unbound of pemigatinib is 4.0%, 8.6%, and 9.4% in rat, monkey, and human, respectively. The blood to plasma radioactivity ratios from excretion studies using 14C-pemigatinib in rats, dogs, and human participants indicate generally minor to no preferential partitioning of pemigatinib-derived radioactivity into blood cells.

The primary clearance pathway of pemigatinib is via metabolism by CYP3A4. Several oxidative and conjugated metabolites of pemigatinib were identified from in vitro and *in vivo* systems.

Figure 2: Observed metabolic pathway of Pemigatinib in rats, dogs and humans

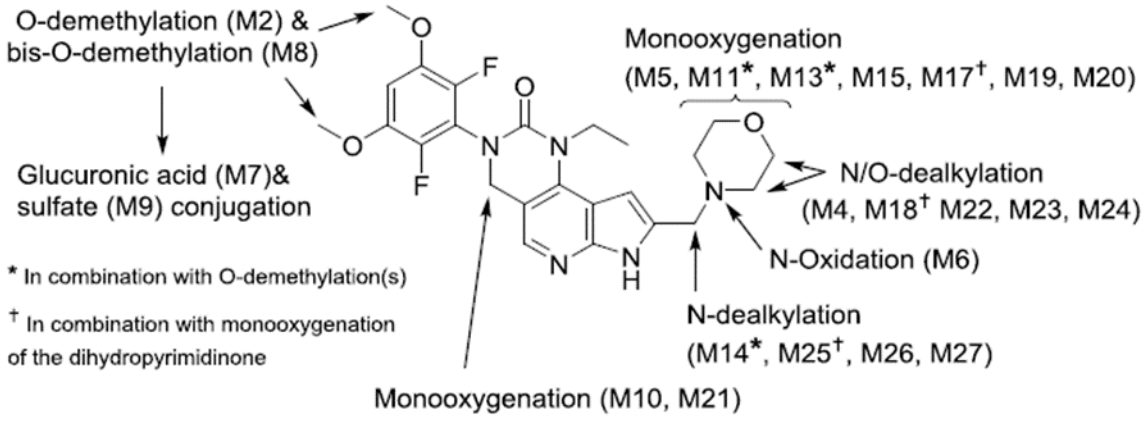


Table 5: Metabolites Characterised in Rats (R), Dogs (D) and Human (H) After a Single Dose of 14C-Pemigatinib

			Species observed			
Designation	***m/ζ***	**Metabolite description**	**Plasma**	**Urine**	**Feces**	**Bile**
M2 (INCB056632)	474	O-desmethyl pemigatinib			**H D R**	
M4	462	Primary alcohol product of morpholine ring oxidative cleavage	**R**	**D R**	**D R**	**D**
M5	520	Dioxygenation of morpholine ring			**H**	**D**
M6 (INCB059898)	504	N-oxide of morpholine ring		**D R**		**D**
M7	650	O-demethylation + glucuronic acid conjugation	**H D R**	**H D**		**D**
M8	460	Bis-O-demethylation			**H**	
M9	554	O-demethylation + sulfate conjugation	**H D R**	**H**		**D**
M10	504	Hydroxylation of dihydropyrimidinone moiety	**H D R**			**D**
M11	474	Bis-O-demethylation + monooxygenation & desaturation of morpholine ring			**H**	
M13	488	O-demethylation + monooxygenation & desaturation of morpholine ring			**H R**	
M14	419	O-demethylation + carboxylic acid resulting from N dealkylation-associated loss of morpholine ring			**H**	
M15	502	Monooxygenation & desaturation of morpholine ring	**H D R**			**D**
M17	520	Monooxygenation of both the dihydropyrimidinone moiety and morpholine ring				**D**
M18	506	Oxidative ring-opened product of morpholine ring + hydroxylation of the dihydropyrimidinone moiety	**R**			
M19	504	Hydroxylation of the morpholine ring	**R**			
M20	536	Multiple oxygenations of the morpholine ring				**D**
M21	502	Oxidation of dihydropyrimidinone moiety to a pyrimidinedione	**D R**			
M22	490	Oxidative ring-opened product of morpholine ring	**D R**			**D**
M23	476	Oxidative ring-opened product of morpholine ring				**D**

In dog and human 14C mass balance studies, elimination of drug-derived radioactivity after oral dosing of pemigatinib was nearly complete. For bile-duct cannulated male dogs given a PO dose, means of 9.52%, 61.9%, and 24.6% of the administered radioactivity were excreted in urine, bile, and faeces, respectively.

Pemigatinib is not a potent reversible inhibitor of the major CYPs evaluated, and there was no evidence of metabolism-dependent inhibition. Results from the plated human hepatocytes assay suggest that pemigatinib was not an in vitro inducer of CYP1A2 and CYP3A4 mRNA. Although there was a potential for pemigatinib to induce CYP2B6 mRNA, it did not induce CYP2B6 functional activity in any of the in vitro donors examined. In vitro study performed to assess the potential induction of pemigatinib on CYP1A2 and CYP3A4 were not acceptable as it did not meet several requirements of the DDI Guideline of 2012. The induction study for CYP1A2, 2B6 and 3A4 was therefore repeated to satisfy all the requirements specific to the EMA guidance. The initial study using plated cryopreserved human hepatocytes assay showed that pemigatinib was not an in vitro inducer of CYP1A2 or CYP3A4 mRNA, but there is a potential for the induction of CYP2B6 mRNA without

accompanying induction CYP2B6 enzyme activity. The results from the repeat study are consistent with those from previous study.

Pemigatinib is a substrate for efflux transporters P-gp and BCRP, but the efflux was saturated at gut concentrations at clinically relevant doses. Pemigatinib is not a substrate for OATP1B1 or OATP1B3. Pemigatinib is not an inhibitor of OATP1B1 or OAT1. Although pemigatinib is an inhibitor of P-gp (IC50 = 4.8 μM), BCRP (> 30 μM), MATE1 (IC50 = 1.1 μM), MATE2K (IC50 = 15.3 μM), OAT3 (IC50 > 33 μM), OCT2 (IC50 = 0.075 μM) and OATP1B3 (IC50 = 3 μM), the potential for pemigatinib to cause clinical drug drug interactions at clinically relevant doses via these transporters is low.

Studies have been conducted to evaluate pemigatinib as a substrate and/or inhibitor of OCT1 and BSEP (DMB-19.204 and DMB-20.23). Results indicate that pemigatinib is not a substrate or an inhibitor for human OCT1. Pemigatinib is neither a substrate, nor a potent inhibitor of human BSEP with IC50> 100 μM.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies with pemigatinib have been conducted in rats and monkeys. Pemigatinib was well tolerated in male and female rats after single oral doses ≤ 10 mg/kg. The maximum tolerated dose (MTD) was 100 mg/kg. Pemigatinib was well tolerated in male and female monkeys following a single oral dose of up to 10 mg/kg. Except a dose-dependent increases noted in serum phosphorous at all dose levels in the monkey study, no other adverse effects were observed.

Repeat dose toxicity

Repeat dose toxicity studies have been performed in rats and monkeys.

Repeat-dose toxicity in rats

A 9-day oral gavage toxicity and toxicokinetic study (0, 5, 10 or 20 mg/kg/day) in Sprague-Dawley Rats showed a poor tolerability at all doses (early termination) and all doses in this study exceeded an MTD. The 9-day oral gavage toxicity and toxicokinetic study in Sprague-Dawley Rats at lower doses (0, 0.3, 0.75 or 2 mg/kg/day) showed a phosphorus increase, an hypertrophy of the femoral growth plate; minimal-to-mild mineralisation of the soft tissue mineralisation (mucosa and muscularis of the glandular and non-glandular stomach, mesenteric, gastric and pulmonary arteries, aorta, and renal distal convoluted tubules and/or corticomedullary junction). The NOAEL was determined to be 0.75 mg/kg/day. An increase in ALT, AST, and cholesterol has also been observed.

In the 28-day oral GLP toxicity and toxicokinetic study with a 28-day recovery period in Sprague Dawley Rats (0, 0.27, 0.54 or 1.05 mg/kg/day), it has been observed in all groups an increase of the mean serum phosphorus levels and a prevalence of bilateral corneal crystals (dystrophy). Tissue mineralisation included minimal-to-mild mineralisation in the renal medullary tubular epithelium, gastric mucosa, submucosal glands of the larynx and corneal epithelium, and increased physeal thickness in the sternum. Tissue mineralisation was not reversed at the end of the 28-day recovery period. Effects on the sternal physis were fully reversed

and thus also not considered adverse. The NOAEL was determined to be 1.05 mg/kg/day, the highest dose tested.

Mineralisation in the cornea consisted of deposits usually the size of only one to two cells at the corneal basement membrane, predominantly in only one eye. Although corneal mineralisation was not noted in any control group animals in this study, the morphological features observed in eyes of animals treated with pemigatinib were consistent with spontaneously occurring corneal dystrophy (Bruner *et al.* 1992) and with those observed in untreated animals following minor trauma to the cornea or dehydration of the cornea associated with other underlying conditions (Greaves *et al.* 2012). The ophthalmoscopic examination revealed corneal crystals in both control and pemigatinib-treated group animals. In rats in the 28-Day and 3-month oral toxicity and bilateral corneal crystals (mineralisation and corneal dystrophy) was observed in all groups and was not reversible.

Regarding the 3-month oral gavage toxicity and toxicokinetic GLP study with a 42-day recovery period in Sprague Dawley Rats (0, 0.27, 0.54, or 1.05 mg/kg/day), administration at 1.05 mg/kg/day was poorly tolerated, resulting in euthanasia of several animals, clinical signs, and body weight loss, leading to early termination of the males and females in this group during study Week 8. Histologic findings of physeal dysplasia, articular cartilage dysplasia, incisor tooth dysplasia, and soft tissue and/or vascular mineralisation were observed in all pemigatinib-treated groups. The soft tissue and vascular mineralisation correlated with higher phosphorus values in the 0.54 and 1.05 mg/kg/day group males and the 0.27, 0.54 and 1.05 mg/kg/day group females and higher calcium values in the 1.05 mg/kg/day group males and females. The physeal dysplasia correlated with gross observations of soft, with nodules, and/or white discoloration of the bone (femur, vertebra) in the 1.05 mg/kg/day group females. A lack of recovery was observed in regards to dysplasia in the incisor teeth, physeal dysplasia and articular cartilage dysplasia in the femur, as well as mineralisation in the kidney. A NOAEL was not determined in this study.

In Monkeys

In the Cynomolgus monkeys, the 10-day oral gavage toxicity and toxicokinetic study (0, 1 or 3 mg/kg/day) revealed that target organs were the kidney (hyperplasia/hypertrophy of proximal and collecting tubular epithelium, renal tubular degeneration and necrosis), heart (mineralisation), stomach, aorta (mineralisation), lungs (mineralisation), ovary (mineralisation), and bone marrow. The main effect was also the tissue mineralisation which was again attributed by the applicant to the pharmacology of pemigatinib. A NOEL was not determined; hyperphosphatemia was noted in all pemigatinib-treated groups. Soft tissue mineralisation in monkeys was observed only at 3 mg/kg/day in the 10-day range-finding study (non-GLP study T13-10-13), and was not assessed for reversibility. The NOAEL was determined to be 1 mg/kg/day.

Minimal mineralisation of the ovary (1F given 1 mg/kg/day and 2F given 3 mg/kg/day) showed that affected follicles appear to be consistent with normally occurring atretic follicles. Because focal or multifocal mineralisation of primary follicles was considered a common, incidental finding in nonhuman primates by the applicant, observations were considered background phenomena. However, the very large number of mineralised primary follicles seen in 2F given 3 mg/kg/day was considered to be treatment related because of the number of primary follicles involved and the severity of the mineralisation.

Hypercellular bone marrow with and without periosteal inflammation was seen in 1M and 2F given 3 mg/kg/day considered pemigatinib-related. One male given 3 mg/kg/day had diffuse mild granulomatous interstitial inflammation of the stomach mucosa of uncertain origin accompanied by a small ulcer and an

epithelial microabscess. An erosion of the gastric mucosa was also seen in 2 other males given 3 mg/kg/day. Minimal-to-mild diffuse vacuolar degeneration of the acinar pancreas was noted in 3 males, but no females given 3 mg/kg/day.

The 28-day oral toxicity and toxicokinetic GLP study with a 28-day recovery period in Cynomolgus Monkeys (0, 0.1, 0.33 or 1 mg/kg/day) showed an elevation of the liver enzymes starting at the lower dose and unilateral lens opacity in one male. Both of the bone (physis) and the eye (lens, retinal vessels) were the target. Femoral physeal dysplasia was noted in animals dosed at ≥ 0.33 mg/kg/day; cartilage dysplasia of the sternal synchondroses was noted only in animals dosed with 1 mg/kg/day; both findings were reversible and therefore considered non-adverse. A single animal dosed at 0.1 mg/kg/day pemigatinib had a chronic fracture of the growth plate. The NOEL was defined as 0.1 mg/kg/day. The NOAEL was considered to be 1 mg/kg/day, the highest dose tested.

In the 13-Week GLP study by oral gavage in Cynomolgus Monkeys with a 6-week recovery period, target organs were bone (physis) and cartilage plates of the sternum with a phosphorus increase. Pemigatinib-related findings included reversible increases in ALT at 1.0 mg/kg/day. Femoral physeal dysplasia and cartilage dysplasia of the synchondroses of the sternum was noted in animals dosed with ≥ 0.1 mg/kg/day that were not present at 0.1 mg/kg/day at the recovery necropsy on Day 136. Based on the character and reversibility of the bone and cartilage findings, a NOAEL was defined as 0.1 mg/kg/day.

In the 28-day monkey study, lens opacities (capsule, posterior) of moderate severity were observed in two male monkeys dosed with pemigatinib at 0.33 and 1 mg/kg/day, and one female monkey dosed with 1 mg/kg/day had slight attenuation of retinal vessels in relation with the administration of pemigatinib. In the 3-month monkey study, there were no ophthalmological findings at the same doses administered over a longer duration.

Genotoxicity

Pemigatinib underwent a complete genotoxicity tests battery *in vitro* and *in vivo*, included the definitive microbial reverse mutation assay, human lymphocyte assay and the *in vivo* rat micronucleus assay. Pemigatinib was negative in the Bacterial Reverse Mutation Assay and did not induce significant structural chromosome aberrations in human lymphocyte cultures when tested up to concentrations that produced marked mitotic suppression (> 45% was observed at doses >48.8 µg/mL) in the presence and absence of metabolic activation.

Clastogenic activity and/or disruption of the mitotic apparatus by counting micronuclei in polychromatic erythrocytes (PCEs) in rat bone marrow was detected but, this number was within the historical vehicle control range.

Carcinogenicity

No carcinogenicity studies were conducted with pemigatinib, in compliance with ICH guideline S9.

Reproduction Toxicity

The reproductive and developmental toxicity of pemigatinib was investigated in a non-GLP dose-range-finding embryo-foetal development study in rats (T18-02-04). Administration of pemigatinib to time-mated rats from Gestation Day 6-17 at doses of 0, 0.1, 0.3 and 1.0 mg/kg/day was associated with decreased foetal growth and malformations (increase in foetal skeletal malformations and major blood vessels variations, reduced ossification and decrease foetal body weight) at 0.1 mg/kg/day and total early postimplantation loss at $\geq$ 0.3 mg/kg/day. The NOEL for effects of pemigatinib on embryo/foetal development was considered to be less than 0.1 mg/kg/day. The AUC-based exposure at this dose group is approximately 0,2-fold the clinical exposure at the maximum recommended human dose of 13.5 mg (AUC0-24=2620nM·h).

Embryo-foetal lethality observed at ≥0.3 mg/kg (≥0.5-fold clinical exposure) precluded further foetal observations. It occurred in absence of clear maternal toxicity (net maternal body weights similar to controls, clinical observations related to postimplantation loss). Examinations conducted on foetuses from dams treated at the non-maternotoxic dose of 0.1 mg/kg (0.2-fold clinical exposure) showed treatment-related skeletal malformations (vertebral anomalies associated with rib anomalies), major blood vessels variations (absent innominate artery), and decreased foetal weights.

No effects on reproductive organs have been observed in repeat-dose toxicity studies with pemigatinib.

No pemigatinib-related findings in male or female reproductive tissues in rats following administration for up to 90 days (more than 1 full spermatogenic cycle) were observed. Specifically, there were no pemigatinib-related microscopic findings in the testes or epididymides indicative of an effect on spermatogenesis, or findings in the ovary indicative of an effect on folliculogenesis, or effects on oestrus cycle based on vaginal staging.

No studies on pre-postnatal development have been conducted with pemigatinib. No studies on the excretion of pemigatinib into breast milk have been conducted in animals and humans and no data on the safety in newborns or infants are available. No juvenile toxicity studies have been performed with pemigatinib.

Prenatal and postnatal development, including maternal function

As per ICH S9 guideline no study has been conducted on prenatal and postnatal development, including maternal function.

Toxicokinetic data

Local Tolerance

As the intended route of administration is oral. The gastrointestinal tract was evaluated in all repeat-dose toxicology studies in Sprague-Dawley rats and cynomolgus monkeys. No dedicated local tolerance testing was conducted.

Other toxicity studies

Studies on impurities

A total of 26 starting materials, process intermediates or potential process impurities were evaluated for potential mutagenicity using Derek Nexus (rule-based expert system) and Sarah Nexus (statistical based methodology) as per ICH M7(R1). Of these, 24 structures were assigned as Class 5 (not genotoxic). Starting material INCB072818 was assigned as Class 3 (genotoxic impurity). An additional structure, INCB081503, was assigned Class 5 within Nexus. However, this compound contained a misclassified feature within Derek. Upon further evaluation of the misclassified feature, there was insufficient information to negate a potential concern for mutagenicity. INCB081503 has not been tested for mutagenicity. Therefore, INCB081503 was reclassified as an ICH Class 3 (genotoxic impurity).

Phototoxicity

INCB054828 absorbs UV light with a peak at 290 nm and shoulder that extends to ~315 nm. The molar extinction coefficient at 290 nm = 18746. Nonetheless, the UV absorption spectrum and molar extinction coefficient for INCB054828, together with higher levels and prolonged residence time in the eye (uvea) and skin observed in a tissue distribution study in pigmented rats vs. non-pigmented rats, meets the criteria for consideration of phototoxicity testing under ICH S10. Pemigatinib did not demonstrate phototoxic potential in an *in vitro* neutral red uptake phototoxicity assay as measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to pemigatinib in the presence of ultraviolet radiation.

Preliminary evaluation revealed a solubility limit of 3.17 µg/mL for INCB054828 in 1% DMSO/Dulbecco's phosphate buffered saline supplemented with Ca2+ and Mg2+ ions (DPBS) at a pH of 7.0 - 7.3. In the range-finding assay, the IC50 for cytotoxicity and phototoxicity was not achieved. The chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes assay also used DMSO as the vehicle. Upon sonication for approximately five minutes, the test article was soluble in DMSO at a concentration of approximately 48.8 mg/mL (maximum concentration) and 3, 10, 20, 30, 40, 50, and 100 µg/mL were the final concentrations.

In the BALB/c 3T3 mouse fibroblasts test, the solvent used was Dulbecco's Phosphate Buffered Saline with Ca2+ and Mg2+ with 1% Dimethyl Sulfoxide, (DPBS/DMSO). 3.17 µg/mL was defined as the maximum concentration due to a limit of solubilisation.

According to the ICH guideline S10 and to the OECD Guidelines for the Testing of Chemicals, Section 4, Test No. 432: *In Vitro* 3T3 NRU Phototoxicity Test, in case of limited solubility of the test chemical and absence of cytotoxicity, a rationale for the highest concentration tested should be provided. For non-cytotoxic chemicals (no IC50 value up to precipitation), it might be useful to demonstrate the solubility limit under assay conditions. In this case, including two or three concentrations in the main experiment that will likely show precipitation may be useful.

Detailed records documenting the receipt, distribution, storage, and disposition of test, article, and vehicle components were provided by the applicant. Moreover, the highest concentration is the accepted limit dose as defined in ICH S10. The IC50 for cytotoxicity and phototoxicity was not defined (i.e., no cytotoxicity was observed). One patient started pemigatinib on 14AUG17 and Grade 1 photosensitive reaction was reported 1 month later (18SEP17), as related to pemigatinib. Given the low severity of the phototoxicity, the issue not further pursued.

2.3.5. Ecotoxicity/environmental risk assessment

In accordance with Article 8 (ECID, 2016) of Directive 2001/83, as amended, and the CHMP guidance (EMEA/CHMP/SWP/4447/00, 01 June 2006) - Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA, 2006) and an associated Questions and Answers Document (EMA, 2016) an environmental risk assessment report is submitted in support of the Marketing Authorisation Application for Pemigatinib.

Table 6: Summary of main study results

Substance (INN/Invented Name): pemigatinib			
CAS-number (if available): 1513857-77-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log P_{OW} = 2.23 ± 0.02 Log D_{OW} at pH range (5-9) ranged from 1.09 to 2.23	Not Potential PBT log D_{OW} ≥ 4.5
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	1.09 to 2.23	not B
	BCF	-	not B
Persistence	DT50 or ready biodegradability	-	not P
Toxicity	NOEC or CMR	-	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined	0.068 (default) 0.001 (refined)	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)	no endocrine activity		

The environmental risk assessment (ERA) stopped in Phase I. Environmental risks are very unlikely as the PECsurfacewater value is below the action limit because of the orphan designation of the medicinal product. No further PBT assessment is required as the log Kow is below 4.5. The ERA is complete and acceptable. Therefore pemigatinib is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pemigatinib is a potent and selective inhibitor of human FGFR1, FGFR2, and FGFR3. It is also selective against VEGFR2 and it has a similar potency for the rat FGFR1 and FGFR2 kinases. It also reduces angiogenesis or lymphangiogenesis, leading to another anticancer activity. The inhibitory potency of pemigatinib was evaluated against VEGFR2 because this non-FGFR kinase was most potently inhibited by pemigatinib**.** Drugs can also affect VEGF-mediated cell proliferation, migration, invasion via blocking VEGFR2/RAF/MEK/ERK and PI3K/AKT pathways in cholangiocarcinoma cell. The non-clinical assessment suggests no potential relevance of inhibition of VEGFR2 by pemigatinib in patients, however no dedicated *in vivo* studies were completed to test this activity. A summary of data on a potential clinical activity of pemigatinib via VEGF2 from clinical trials subjects has been provided by the applicant. Non-clinical assessment suggests no potential relevance of inhibition of VEGFR2 by pemigatinib in patients. From a clinical

perspective, the low frequency of some safety events as hypertension, pulmonary embolism, proteinuria, rectal haemorrhage, or even gastrointestinal haemorrhage and the fact that patients had advanced disease and significant baseline comorbidities, which are confounding factors, indicate that the clinical significance of VEGFR2 inhibition by pemigatinib might be minor. Moreover, reduced levels of soluble VEGFRs and increased VEGF levels have not been observed.

Pemigatinib inhibited autophosphorylation of FGFR proteins in cancer cell lines displaying activated FGFR1, 2 and 3 and phosphorylation of key downstream signalling components of the FGFR signalling pathways in KG-1A cells (i.e. ERK1/2, and STAT5). FGF/FGFR fundamentally regulates embryogenesis, angiogenesis, tissue homeostasis, and wound repair. It also plays important roles in diverse cell functions, including proliferation, differentiation, apoptosis and migration. Downstream signalling pathways included the mitogen activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), the phosphoinositide-3-kinase (PI3K)/Akt pathways, and DAG-PKC and IP3-Ca2+ signalling branches via PLCγ activation.

Administration of pemigatinib, i.e. FGFR inhibition, actively induces a compensatory upregulation of the markers FGF21, FGF23 and CHRDL2. Physiologically, FGF23 plays a role as a bone-derived mediator of phosphate homeostasis in which both phosphate and FGFR signalling induce FGF23 expression (Wöhrle et al 2011). Continuing FGF-23 elevation even after drug pause was measured in the study patients and this seems to be contributing to the continuously observed hyperphosphataemia. Thus, despite the very few data from cohort C it can be deduced that the compensatory upregulation of FGF-23 is also present in CCA patients lacking the target FGFR2 rearrangements and fusions (as in cohort C which patient with CCA negative for oncogenic FGF/FGFR mutations were included). This means that such patients suffer from adverse effects of pemigatinib like hyperphosphateaemia while obviously lacking clinical benefit. This patient population should therefore not be treated with pemigatinib (see FGFR 2 fusion positivity status requirements in section 4.2 of the SmPC).

Mutational data were available for 2 of the 3 patients, with 1 having no reported FGF/FGFR alterations and the other having a variant of unknown significance in FGFR2 with no literature data supporting that this was an activating alteration. The most frequent alterations detected in patients in Cohort C were CDKN2A, KRAS, IDH1, ARID1A, CDKN2B, and TP53.

In vivo, pemigatinib demonstrated antitumour activity in rodents bearing tumours derived from multiple human cancer cell lines with FGFR1, 2, and 3 alterations (translocation or amplification) including gastric, cholangiocarcinoma, bladder, and in a mouse study using patient-derived xenografts originated from blood expressing FGFR1 fusion protein.

Furthermore, the binding behaviour of pemigatinib has been further discussed and the applicant's conclusion that pemigatinib is an ATP competitive inhibitor of FGFR1 is agreed. ATP-binding plays an essential role for receptor activity and the kinase domains of FGFRs are highly homologous.

Safety studies addressing respiratory and CNS effects revealed no effects. Piloerection in a single 10 mg/kg male rats and increased touch response in a single 10 mg/kg male and female were considered potentially pemigatinib-related, but not adverse. Lower respiratory frequency in rats (1.5 and 10 mg/kg) during the initial 0-15 minute postdose period and higher (14.6%) respiratory frequency (10 mg/kg) for the individual subphase from 316-330 minutes postdose were observed but considered as not biologically relevant based on their relatively small magnitude and short duration of the effects.
In monkeys, qualitative changes in ECG were noted but premature atrial conduction and premature ventricular contractions were not considered to be the result of pemigatinib administration due to the

sporadic nature of the findings, presence of findings in the same animals following administration of the vehicle, and the lack of any dose response relationship.

The absorption, distribution, metabolism, and excretion of pemigatinib were studied in Sprague Dawley rats, cynomolgus monkeys, and beagle dogs. The oral bioavailability was moderate in monkeys (29%), and complete in rats and dogs. Pemigatinib exhibits a low to moderate volume of distribution in all 3 species. Pemigatinib has limited penetration across the blood brain barrier in rodents. The primary clearance pathway of pemigatinib is via metabolism by CYP3A4. In dog and human 14C mass balance studies, elimination of drug-derived radioactivity after oral dosing of pemigatinib was nearly complete.

The presence of multiple metabolites and minimal excretion of unchanged parent in excreta indicate that the primary clearance pathway of pemigatinib is metabolism.

Pemigatinib is not a potent reversible inhibitor of the major CYPs evaluated, and there was no evidence of metabolism-dependent inhibition. Results from the plated human hepatocytes assay suggest that pemigatinib was not an *in vitro* inducer of CYP1A2 and CYP3A4 mRNA. Pemigatinib is a substrate for efflux transporters P-gp and BCRP, but the efflux was saturated at gut concentrations at clinically relevant doses. Pemigatinib is not a substrate for OATP1B1 or OATP1B3. Pemigatinib is not an inhibitor of OATP1B1 or OAT1. Although pemigatinib is an inhibitor of P-gp (IC50 = 4.8 µM), BCRP (> 30 µM), MATE1 (IC50 = 1.1 µM), MATE2K (IC50 = 15.3 µM), OAT3 (IC50 > 33 µM), OCT2 (IC50 = 0.075 µM) and OATP1B3 (IC50 = 3 µM), the potential for pemigatinib to cause clinical drug drug interactions at clinically relevant doses via these transporters is low. As well Pemigatinib is neither a substrate, nor a potent inhibitor of human OCT1 or BSEP.

The toxicology programme is conducted under the guideline ICH S9 (ICH 2009) for advanced cancer, as well as all other relevant ICH Guidelines related to nonclinical safety which is considered acceptable regarding the claimed indication.

Single dose toxicity studies with pemigatinib have been conducted in rats and monkeys. Pemigatinib was well tolerated in male and female rats after single oral doses ≤ 10 mg/kg.

In repeat-dose toxicity, the administration scheme is acceptable to cover the exposure in all studies. The route used in all toxicological studies is the same as the one used clinically which is acceptable.

The most prominent findings following repeat-dose administration of pemigatinib in both rats and monkeys were attributed to the intended pharmacology of pemigatinib (FGFR1, FGFR2, and FGFR3 inhibition), including hyperphosphatemia, physeal dysplasia, and soft tissue mineralisation. Mineralisation was observed in numerous tissues including kidneys, stomach, arteries (gastric and pulmonary), ovaries (monkey only), and eyes (cornea; rat only). Based on the incidence in control group animals, the minimal-to-mild nature of the findings and reports of most of these conditions as spontaneous conditions in control animals (Bruner *et al.* 1992), it is likely that the increased incidence of mineralisation in various tissues represented a pemigatinib-related exacerbation of a spontaneously occurring condition. All microscopic changes were considered secondary to the pharmacological activity of pemigatinib. Soft tissue mineralisation was not reversible, while physeal and cartilage findings were reversible. In addition, changes of the bone marrow were observed. These are reflected in SmPC section 5.3.

Provided historical data show that the background incidence of lens opacities in monkeys and corneal crystals in rats are consistent with the incidence of these findings in toxicology studies with pemigatinib.

In general, the increases in phosphorus observed in rats and monkeys were relatively small (< 2-fold) and reversible, and similar between the two species. There were no meaningful changes in calcium levels in monkeys or rats in the 90-day studies.

Increased incidence of mineralisation in various tissues at these doses represents a pemigatinib-related exacerbation of a spontaneously occurring condition. Moreover, soft tissue mineralisation was not reversible during the 28-day recovery period.

There are no safety margins for the soft tissue mineralisation in rats and monkeys and ophthalmic findings for up to 90 days. Moreover, clinical experience with pemigatinib suggests that soft mineralisation are rare but do occur. The knowledge that mineralisation is related to the pharmacology of FGFR inhibition and the fact that it was observed in animal studies in the heart, lungs, aorta, and other soft tissues suggests that FGFR inhibition in humans might produce similar effects which is in agreement with the non-existent safety margin .

Pemigatinib produced functional effects in the kidney, indicated by BUN and creatinine increases, at high dose that were not tolerated; adverse clinical observations and marked body weight loss required early animal euthanasia after 3-4 days of dosing.

The repeat dose studies suggest that there is no evidence of heart and aorta mineralisations in cynomolgus monkeys after up to 90 days of continuous dosing at up to 1 mg/kg/day. Serum calcium levels were unaffected in these studies. Results of cardiovascular safety pharmacology study do not support the link between the premature atrial conduction and premature ventricular contractions and pemigatinib administration.

Ocular toxicity and dose- and time dependent mineralisation of soft tissues occurred in both rats and monkey studies at different doses. The findings do not seem to be reversible and no safety margin with regard to the possible clinical relevance was presented.

Significant non-clinical findings exist with respect to soft tissue mineralisation, ophthalmic findings and nephrotoxicity. These effects observed during non-clinical studies are likely to occur in humans and should be monitored appropriately. Relevant dose modifications and warnings are included in section 4.2 and 4.4 of the SmPC.

In the view of results, the genotoxicity characteristic of Pemigatinib could be considered as negative. No carcinogenicity studies were conducted with pemigatinib, in compliance with ICH guideline S9.

FGF ligands and FGFRs are widely expressed during development, and FGF FGFR signalling is essential during embryonic development. Based on the mechanism of action of pemigatinib (inhibitor of FGFR1-3), the effects on embryo-foetal development seen in rats are expected. These effects should be regarded as relevant for humans and pemigatinib may be classified as a suspected human teratogen. No studies on fertility and early embryonic development have been performed with pemigatinib. Due to the indication of pemigatinib and the teratogenic effects observed in the range-finding embryo-foetal toxicity study, the lack of fertility and early embryonic developmental studies is acceptable and is in line with the recommendations given in the ICH S9 guideline. Relevant wording is reflected in SmPC section 4.4 and 4.6.

No effects on reproductive organs have been observed in repeat-dose toxicity studies with pemigatinib. Nevertheless, data from the literature reported that FGFs and FGFRs are present in both female and male reproductive tissues of several species, including humans, where they contribute to regulate the reproductive

function. Based on the pharmacology of pemigatinib, impairment of male and female fertility cannot be excluded.

No studies on pre-postnatal development have been conducted with pemigatinib. The lack of pre-postnatal developmental studies is acceptable in view of the intended indication for Pemazyre and is in line with the ICH S9 guideline.

It is unknown whether pemigatinib is excreted into human breast milk. Since FGF signalling is involved in several physiological developmental processes, a risk to the suckling child cannot be excluded. There are no human and animal data on the excretion of pemigatinib and or its metabolites into breast milk. Furthermore, no data on the safety in newborns or infants are available. The recommendation to discontinue breast-feeding during treatment and for 1 week following completion of therapy is considered acceptable, considering the lack of data of milk excretion, the toxicology profile and the mean elimination half-life of 15.4 hours of pemigatinib (see SmPC section 4.6).

Since the currently intended indication of Pemazyre is for treatment of adults, the lack of juvenile toxicity studies in animals is acceptable; pemigatinib was granted a full paediatric waiver for development for the treatment of either cholangiocarcinoma or urothelial carcinoma (EMA decision P/0386/2018).

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the MAA for Pemazyre is approvable.

Significant non-clinical findings exist with respect to soft tissue mineralisation, ophthalmic findings and nephrotoxicity. These effects observed during non-clinical studies are likely to occur in humans and should be monitored appropriately. Relevant warnings are included in section 4.4 of the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 7

Study Identifier (Type of Study); Location of Study Report	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s) Dose Regimen(s) [a] ; Route of Administration**	**Number of Participants Enrolled and Countries**	**Healthy Participants or Diagnosis of Participants**	**Duration of Treatment**	**Study Status; Type of Report**
Phase I trials -PK in healthy volunteers and patients, Tolerability and Safety, DDI, Safety in Japanese Patients (additional trials planned in renal and hepatic impairment)							
INCB 54828-105 (Healthy Participant PK and Tolerability) 5.3.3.1	PK (mass balance and metabolite profile of pemigatinib)	Phase 1, open-label **ADME study**	Pemigatinib 11 mg PO followed 10 minutes later by an oral dose solution of approximately	7 US	Healthy participants	Single dose	Completed ; Final
INCB 54828-101 (Patient PK and Initial Tolerability) 5.3.3.2	Safety, tolerability, PK, pharmaco-dynamics	Phase 1/2, open- label, multicentre, uncontrolled , dose-escalation and expansion study	Part 1: pemigatinib 1, 2, 4, 6, 9, 13.5, or 20 mg QD on a 2-weeks-on/1-week-off (intermittent) schedule or 9, 13.5, or 20 mg QD on a continuous schedule; PO Part 2:	160 US, Denmark	Advanced malignancies	~6 months	Ongoing; Interim
INCB 54828-102 (Patient PK and Initial Tolerability) 5.3.3.2	Safety, tolerability, PK, pharmaco-dynamics	Phase 1, open-label, multicentre, uncontrolled, dose-escalation and dose-	Part 1 (dose escalation): Pemigatinib 9 or 13.5 mg QD on an intermittent schedule; PO Part 2 (dose	25 Japan	Japanese participants with advanced malignancies	~6 months	Ongoing; Interim
INCB 54828-107 (Patient PK and Initial Tolerability) 5.3.3.3	PK, safety	Phase 1, open-label study	Pemigatinib 9 mg single dose PO	40 (planned) US	Healthy participants and participants with hepatic impairment	Up to 2 months	Ongoing; N/A
INCB 54828-108 (Patient PK and Initial Tolerability)	PK, safety	Phase 1, open-label study	Pemigatinib 9 mg single dose PO	48 (planned) US	Healthy participants and participants with renal impairment	Up to 2 months	Ongoing; N/A

Study Identifier (Type of Study); Location of Study Report	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s) Dose Regimen(s) [a] ; Route of Administration**	**Number of Participants Enrolled and Countries**	**Healthy Participants or Diagnosis of Participants**	**Duration of Treatment**	**Study Status; Type of Report**
INCB 54828-104 (Extrinsic Factor PK) 5.3.3.4	Effect of itraconazole and rifampin on pemigatinib PK	Phase 1, open-label, **DDI study**	Cohort 1: pemigatinib 4.5 mg single dose PO in a fasted state on Day 1; itraconazole 200 mg QD PO in a fed state on Days 4 to 7 and Days 9 to 11; pemigatinib 4.5 mg single dose PO and itraconazole 200 mg single dose	36 US	Healthy participants	Cohort 1: ~12 days Cohort 2: ~13 days	**Completed; Final**
INCB 54828-106 (Extrinsic Factor PK) 5.3.3.4	Effect of esomeprazole and ranitidine on pemigatinib PK	Phase 1, open-label, **DDI study**	Cohort 1: pemigatinib 13.5 mg single dose PO in a fasted state on Day 1; esomeprazole 40 mg QD PO in a fed state on Days 3 to 7; pemigatinib 13.5 mg single dose PO and esomeprazole 40 mg single dose	35 US	Healthy participants	Cohort 1: ~9 days Cohort 2: ~7 days	Completed; Final
Phase II (uncontrolled trial - claimed as pivotal for this application)							
INCB 54828-202 (Uncontrolled Clinical Study) 5.3.5.2	**Efficacy, safety, tolerability**	**Phase 2, open-label, single-arm, multicentre study**	**Pemigatinib 13.5 mg QD on an intermittent schedule; PO**	**146 US, South Korea, UK, France, Italy, Thailand, Germany, Belgium, Israel, Spain, Japan**	**Participants with advanced/metastatic or surgically unresectable cholangiocarcinoma who have progressed after at least 1 previous systemic treatment**	**~6 months**	**Ongoing; Interim**
Phase II (uncontrolled trials in other indications, urothelial carcinoma and myeloid/lymphoid neoplasms)							
INCB 54828-201 (Uncontrolled Clinical Study) 5.3.5.2	Efficacy, safety, and tolerability	Phase 2, open-label, multicentre, uncontrolled study	Pemigatinib 13.5 mg on an intermittent or continuous schedule; PO	184 US, Denmark, France, Italy, Israel, Spain, Belgium, UK, Japan, Germany,	Participants with metastatic or surgically unresectable urothelial carcinoma harboring FGF/FGFR alterations	~6 months	Ongoing; Interim

Study Identifier (Type of Study); Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dose Regimen(s) [a] ; Route of Administration	Number of Participants Enrolled and Countries	Healthy Participants or Diagnosis of Participants	Duration of Treatment	Study Status; Type of Report
INCB 54828-203 (Uncontrolled Clinical Study) 5.3.5.2	Efficacy, safety, and tolerability	Phase 2, open-label, multicentre, uncontrolled study	Pemigatinib 13.5 mg QD on an intermittent or continuous schedule; PO	15 US, Canada, Germany, Italy, Spain, UK, Austria, France, Switzerland (some	Participants with myeloid/lymphoid neoplasms with 8p11 rearrangement known to lead to FGFR1 activation	~6 months	Ongoing; Interim
Phase III trial (planned and started)							
INCB 54828-302 (Controlled Clinical Study) 5.3.5.1	Efficacy and safety of pemigatinib versus gemcitabine plus cisplatin chemotherapy in first-line treatment of participants with unresectable or metastatic cholangio-carcinoma with FGFR2 rearrangement	Phase 3, open-label, randomised, active-controlled study	Group A: Pemigatinib 13.5 mg QD on a continuous schedule PO – may titrate to 18 mg QD Group B: Gemcitabine 1000 mg/m2 + cisplatin 25 mg/m2 IV on Days 1 and 8 of each 3-week cycle for up to 8 cycles - may cross over to pemigatinib if chemotherapy is	Planned:432 Recruited: Austria, Belgium, Finland, France. Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom, United	Participants with advanced/ metastatic or surgically unresectable cholangiocarcinoma with FGFR2 rearrangements who have not received prior anticancer systemic therapy	~12 months	Ongoing; N/A

2.4.2. Pharmacokinetics

Pharmacokinetics of pemigatinib following single oral dosing are available from three completed phase 1 studies in healthy participants: a 14C-labeled mass balance study (INCB 54828-105), interaction studies with CYP3A4 inhibitor or inducer (INCB 54828-104) and gastric pH modifying agents (INCB 54828-106). Additionally, the PKs of pemigatinib following multiple-dose administration are available in all-comer cancer participants (INCB 54828-101 and INCB 54828-102) as well as participants with cholangiocarcinoma (INCB 54828-202). These later studies in patients are still ongoing and interim CSR for each of the studies are included in this MAA.

A summary of the clinical pharmacology programme is provided in Table 8. Also, a Phase 3 study (INCB 54828-302) in participants with cholangiocarcinoma who have not received prior anticancer systemic therapy is ongoing. Data from this study is not submitted.

Table 8: Clinical pharmacology studies with pemigatinib

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen*; Drug Product Batch Number	Number of Participants	Healthy Participants or Diagnosis of Participants	Duration of Treatment	Study Status
INCB 54828-104	Effect of itraconazole (a potent CYP3A4 inhibitor) or rifampin (a potent CYP3A4 inducer) on pemigatinib PK	Open-label, fixed sequence, single-dose pemigatinib and multiple-dose itraconazole (cohort 1) or rifampin (cohort 2)	Pemigatinib tablet 4.5 mg; Dose: Pemigatinib 4.5 mg and itraconazole 200 mg QD (cohort 1); Pemigatinib 13.5 mg and rifampin 600 mg QD (cohort 2) Batch: 160209	36	Healthy Participants	Single doses	Completed
INCB 54828-105	Route of elimination and mass balance; metabolite profile and PK	Open-label mass balance study	Pemigatinib 4.5 mg and 2 mg tablet and oral solution of [^{14}C]pemigatinib (19 µCi/mg); Dose: two 4.5 mg and one 2 mg tablets of pemigatinib followed by an oral solution of [^{14}C]pemigatinib (250 µCi ~ 2.1 mg) Batch: 160113 (2 mg), 160209 (4.5 mg)	7	Healthy Participants	Single dose	Completed
INCB 54828-106	Effect of esomeprazole (a proton pump inhibitor) and ranitidine (a histamine-2 antagonist) on pemigatinib PK	Open-label, fixed sequence, single-dose pemigatinib and multiple-dose esomeprazole (cohort 1) or ranitidine (cohort 2)	Pemigatinib 4.5 mg tablet; Dose: Pemigatinib 13.5 mg and esomeprazole 40 mg QD (cohort 1); Pemigatinib 13.5 mg and ranitidine 150 mg Q12h (cohort 2) Batch: 160209	35	Healthy Participants	Single doses	Competed
INCB 54828-107	Effect of hepatic dysfunction on pemigatinib PK	Open label, single dose study	Pemigatinib 4.5 mg tablet; Dose: Pemigatinib 9 mg; Batch: 160114	24	Healthy participants and those with varying degrees of hepatic dysfunction	Single dose	Competed
INCB 54828-108	Effect of renal impairment and hemodialysis on pemigatinib PK	Open label, single dose study	Pemigatinib 4.5 mg tablet; Dose: Pemigatinib 25 mg; Batch: 160114	16	Healthy participants and participants with varying degrees of renal impairment	Single dose	Competed

Bioanalysis

Pemigatinib plasma concentration were determined using a validated liquid chromatography with tandem mass spectrometry, with INCB055074 as internal standard. INCB055074 have a similar chemical structure to that of pemigatinib.

The calibration range consisted of 10 levels from 1 to 1000 nM with 5 QC levels 1/3/50/800/1000 with LLOQ and ULOQ set at 1 and 1000 nM, respectively. An additional QC level of 10000 nM was considered. Accuracy, precision, selectivity, reproducibility, matrix effect, recovery, carry-over and stability (short and long-term) have been investigated with satisfactory results.

ISR were planned for PK samples from the three clinical studies (Study INCB 54828-101, 102 and 202), however ISR were performed only for Study 101 and Study 102. For these studies ISR results were satisfactory, therefore the issue (lack of ISR samples from study 202) will not be pursued, the developed bioanalytical method is considered reproducible.

Pharmacokinetic analyses

For single-dose studies, PK parameters evaluated include Cmax, Tmax, AUC0-t, AUC0-∞, T1/2, λz, CL/F, and Vz/F. For multiple-dose studies, PK parameters evaluated include Cmax, Tmax, Cmin, AUC0-τ, T1/2, CL/F,

Vz/F, Ae, CLr, and fe. Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters using Phoenix® WinNonlin version 7.0 or higher (Certara, Princeton, NJ).

Additionally, a population (Pop) PK and PK/PD analyses were conducted based on the non-linear mixed effects modeling. The Pop PK estimation was performed using the first-order conditional estimation with interaction (FOCEI) method implemented in NONMEM 7, version 7.4.1.

The population PK analysis were performed on pemigatinib plasma concentration data collected in Studies (INCB 54828-101; INCB 54828-102; INCB 54828-202) using NONMEM (v7.4, ICON Development Solutions, Ellicott City, MD).

Sparse PK samplings were collected in Study INCB 54828-202 and rich PK samplings were used in Study INCB 54828-101 and Study INCB 54828-102.

Absorption

Formal clinical investigation results (mass balance study INCB 54828-105), supports a fairly high degree (≥85%) of absorption of pemigatinib in humans. The overall recovery of radioactivity was high (95.1% ± 2.81%), with 82.4% ± 3.73% of the dose recovered in faeces and 12.6% ±1.25% recovered in urine. According to the applicant, the faeces metabolite profiling (over the of 1- to 144-hour collection period), 44.4% of the dose was recovered as O-desmethyl- pemigatinib and several other phase I metabolites accounting for 1.6% to 7.1% of dose, while unchanged parent pemigatinib comprised only 1.4% of the administered dose) indicates that the absorbed fraction of pemigatinib is nearly complete. As well, based on faecal metabolite profiling (presence of the M2 metabolite in faeces as a result of absorption, metabolism and intestinal secretion or biliary excretion) from the human mass balance excretion study, the oral absorption of pemigatinib is considered nearly complete. To rule out the possibility that this metabolite is generated by intestinal flora from unabsorbed pemigatinib, particularly as M2 was not detected in plasma, pemigatinib was incubated with human faeces and metabolite profiling of the incubation samples showed no M2 formation from pemigatinib.

After single or multiple dose administration of pemigatinib in both healthy subjects and patients with advanced malignancies, median T_{max} ranged between 1 to 2 hours indicating that absorption is rapid.

In vitro investigations (Caco-2 cell studies) showed a high permeability for pemigatinib across cells (efflux ratio 11×10^{-6} cm/sec at 50μM). Even if pemigatinib (at 1 μM) was found to be substrates of P-glycoprotein and breast cancer resistance protein (BCRP), the efflux mediated by P-gp and BCRP was saturated at concentrations of 1 and 30 μM, respectively. Therefore, it is unlikely that efflux by these 2 transporters plays an important role in the oral absorption of pemigatinib at clinically relevant doses. The mechanism of absorption appears to be mainly driven by passive diffusion.

The absolute bioavailability of pemigatinib has not been evaluated in humans.

Two additional pemigatinib tablet strengths (9 mg and 13.5 mg) have been developed and are proposed for commercial use in addition to the 4.5 mg tablet strength used in the pivotal studies (INCB 54828-101 and 202) and most of clinical pharmacology studies (i.e human ADME Study INCB 54828-105). However, there is no clinical exposure data available for these strengths. The applicant requested a waiver for *in vivo* bioequivalence studies for pemigatinib 9 mg and 13.5 mg tablets. This bridging approach is supported by:

a) The three strengths of tablets are manufactured by the same manufacturing process;

b) The qualitative composition of the two additional strengths (9 and 13.5 mg) is the same than for the 4.5 mg
c) Both the 9 and 13.5 mg strengths are proportionally similar in their active and inactive ingredients to the 4.5 mg strength;
d) Adequate *in vitro* studies show that the dissolution profiles between the highest and lower strengths are similar in three different media. Indeed, rapid dissolution at low pH of 1.2 (0.1 N HCl) with greater than 85% of the active released within 5 minutes for all three strengths and f2 values between 50 and 100 generated in the media investigated at elevated physiological pH (pH 4.5 acetate buffer and pH 6.8 phosphate buffer) which suggests that the dissolution profiles are similar;
e) Linear pharmacokinetics have been demonstrated over the dose range of 4,5 to 13,5 mg; consistent with the rapid and near complete absorption profile of pemigatinib.

As outlined by the EMA Guideline on the Investigation of Bioequivalence (20 January 2010), these criteria met the general biowaiver requirements where a waiver for additional strength(s) is claimed. Also, it is important to note that the two higher strengths are within the dose range studied in clinical trials. Indeed, even when only the 4.5 strength was tested, the administered dose in pivotal studies (INCB 54828-101 and 202) were 9 and 13.5 mg given respectively as two and three tablets of 4.5 mg. Therefore, the awaited systemic exposures levels with the 9 and 13.5 mg dose are already investigated. Overall, it is agreed that no *in vivo* bioequivalence study is deemed to be necessary for the 9 and 13.5 tablets.

In Part 2 of the phase 1/2 study INCB 54828-101, the food effect on pemigatinib PK was evaluated in a small cohort (n=12) of patients with advanced malignances who were administered 13.5 mg pemigatinib in a QD dosing in the fasted (C1D14) and fed (C2D14) state. Even though this sub-study was not powered to draw solid statistical conclusions, PK results indicated that the geometric mean of pemigatinib $C_{max,ss}$ decreased moderately by 18% and $AUC_{0-24,ss}$ increased by only 11% pemigatinib geometric mean after administration of a high-fat and high-calorie meal. The geometric mean ratio (90% CI) of Cmax,ss and AUCss,0-24 was 0.817 (0.648, 1.03) and 1.11 (0.935, 1.31), respectively. In the fed state, median Tmax was delayed to 4.02 hours postdose. Based on these data, pemigatinib tablets could be administered without regards to food and the proposed dosing recommendation with regards to food could be supported.

Distribution

Based on *in vitro* investigations (DMB-14.71.1 and DMB-19.61.1), pemigatinib was found to be highly bound (88.7 to 89.1%) to human plasma proteins. The unbound fraction was independent of pemigatinib in the range of 1 to 30 µM. In addition, pemigatinib was found to bind predominantly to the albumin component of human serum and minimally to α1− acid glycoprotein.

In the human ADME study, the blood-to-plasma radioactivity ratios of Cmax and AUC0-t were determined to be 0.805 and 0.827, respectively, suggesting lack of meaningful distribution of pemigatinib into blood cells.

Following repeated administration of pemigatinib in patients with advanced malignancies (study INCB 54828-101), the geometric mean of Vz/F of pemigatinib was estimated at 173 – 244 L for the dose range of 6 to 20 mg. This suggest an extensive tissue distribution of pemigatinib. This finding of large distribution was confirmed by the population PK analysis of pemigatinib in both patients with cancer and patients with cholangiocarcinoma. The Pop PK approach indicated a large central (Vc/F) and peripheral (Vp/F) apparent volume of distribution of respectively 161 and 80,1 L. Similar finding of large Vz/F ranging from 256 to 305 L was also observed in healthy subjects after single pemigatinib dose of 13 mg (ADME study INCB 54828-105)

and 13.5 mg (please refer to DDI studies INCB 54828-104 and INCB 54828-106). Overall, PK data suggest an extensive distribution of pemigatinib into the extra vascular tissues.

Metabolism

Pemigatinib appears to undergo extensive metabolism, with only 1% and 1.4% of an orally administered dose recovered as unchanged pemigatinib in urine and faeces, respectively. Several metabolites were identified in faeces, urine and plasma. Briefly, in feces, 44.4% of the dose was recovered as M2 (O-desmethyl-pemigatinib) and five additional phase I metabolites (M5, M8, M11, M13, M14) were also detected and, accounting for 1.6% to 7.1% of dose each. In urine, two phase II metabolites (M7 and M9) were detected at levels of 4.4% and 2.1% of the administered dose, respectively. In plasma, several minor circulating metabolites (M7, M9, M10 and M15) were also detected accounting for 5.0% to 6.8% of dose each. Overall, the qualitative metabolite profile of pemigatinib in human was similar to those in preclinical species, thus no human specific metabolites were identified.

In plasma, the parent compound accounted for 64.5% of the total radioactivity, with no major metabolites (≥ 10% of total compound-related material) were detected. This finding is in line with the high ratios of pemigatinib to total radioactivity for Cmax (0.737) and AUC0-t (0.682). In addition, the observed Tmax (2 hours) and terminal half-life (around 10 hours) for total radioactivity in blood and plasma and for pemigatinib in plasma were also found to be similar. Overall, data indicate that pemigatinib is the major circulating component in plasma.

Based on *in vitro* investigations using human recombinant CYP enzymes, pemigatinib was found to be predominantly metabolised by CYP3A4. This finding appears to be in agreement with the experimental results using human liver microsomes and selective chemical inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, showing that the metabolism of pemigatinib was only inhibited by ketoconazole, a potent CYP3A4 inhibitor. The *in vitro* metabolism of pemigatinib using human hepatic microsomes or S-9 systems was moderate with turnover of ~ 45%. In addition, there were no human-specific metabolites and glutathione-related conjugates found in the study.

Elimination

The excretion and biotransformation of $^{[14C]}$pemigatinib were investigated in formal ADME study (INCB 54828-105) in 7 male healthy subjects following a single oral dose of 13 mg/250 µCi (two 4.5 mg tablets and one 2 mg tablet of pemigatinib followed 10 minutes later by an oral dose solution of approximately 250 µCi, or about 2 mg of [14C] pemigatinib). The overall recovery of radioactivity in this mass balance study was high (95.1% ± 2.81%), with 82.4% ± 3.73% of the dose recovered in feces and 12.6% ±1.25% recovered in urine. In addition, renal clearance of pemigatinib was found to be low (0.2 L/hr =3.33 mL/min) corresponding to an unbound renal clearance of 35.4 mL/min (taken into account the plasma free fraction of 9.4%) and suggesting renal clearance via glomerular filtration and reabsorption. This low renal clearance was also confirmed in patients with advanced malignancies receiving pemigatinib as monotherapy (n= 28). Indeed, the geometric mean of renal clearance was 0.208 L/h and fraction of dose excreted in urine was 1.93%. Overall, these data indicate that the biliary clearance rather than the renal route is the major elimination route for pemigatinib. Excretion was relatively rapid, with most of the administered radioactivity (83.5%) was recovered in the first 96 hours postdose.

Across healthy subject studies (including DDI studies presented later in the DDI part) following single oral dose, the geometric mean terminal half-life for pemigatinib was in the range of 9.7 to 12.7 hours. Briefly, the mean terminal half-lives of pemigatinib were estimated to 9.8 hours in ADME study INCB 54828-105 (n= 7, dose = 13 mg) to 11.8 and 12.7 hours in cohorts of pemigatinib alone in DDI study INCB 54828-104 (n= 36, doses = 4,5 and 13,5 mg respectively) and 10.2 and 11.9 hours in cohorts of pemigatinib alone in DDI study INCB 54828-105 (n= 35, dose = 13.5 mg). The mean apparent clearances (CL/F) for pemigatinib in healthy volunteers were estimated between 14.5 to 19.1 L/h.

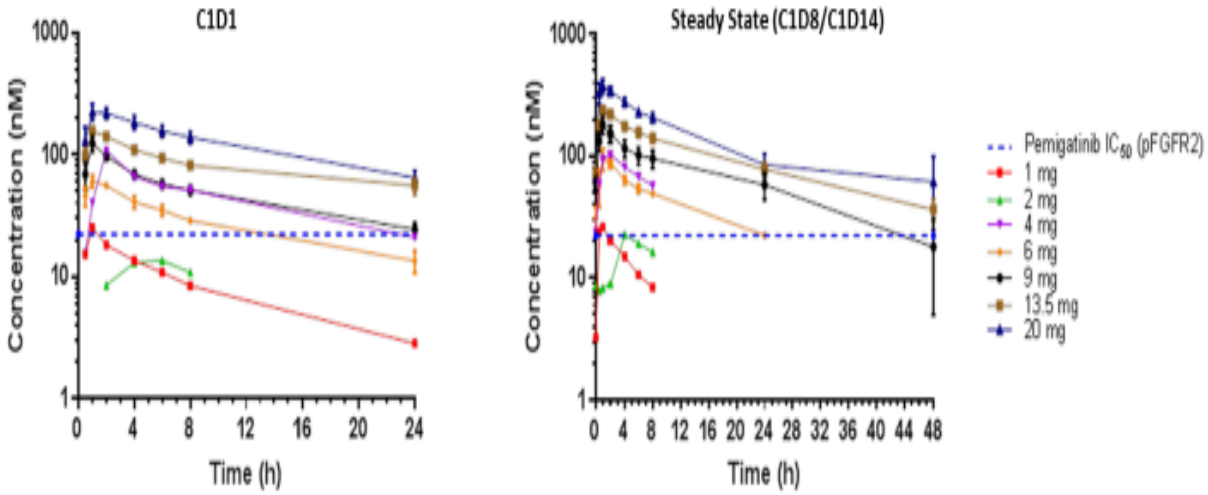
In patients with advanced malignances, a longer elimination half-life was observed after repeated oral QD dosing. For illustration, the geometric mean terminal half-live, based on NCA estimation, was 15.4 hours in phase 1/2 study INCB 54828-101. Similarly, based on the population PK approach, the geometric mean of $T_{1/2}$ were 12.7 hours in INCB 54828-102, 16.1 h in INCB 54828-101 and 14.8 h in INCB 54828-202, patients with cholangiocarcinoma. Consistently with the 40 to 50% longer $T_{1/2}$ in patients, a lower clearance CL/F (around 40 to 50%) was observed in patients compared to healthy subjects; the geometric mean of CL/F for patients with advanced malignancies was in the range of 10.5 to 12.0 L/h. As similar Vd/F was observed between the two populations, this suggest a lower intrinsic clearance for patients with advanced malignancies.

Dose proportionality and time dependencies

Dose proportionality

Figure 3 shows pemigatinib plasma concentrations (mean ± SE) versus time profile after QD dosing of pemigatinib as monotherapy in C1D1 and C1D14. Table 9 summarises the pemigatinib PK parameters after once daily dosing of pemigatinib as monotherapy on C1D1. Table 10 summarises the pemigatinib PK parameters after QD dosing of pemigatinib as monotherapy on C1D14 and the p-values on dose from the 1-factor ANOVA.

Figure 3: Pemigatinib Plasma Concentrations (Mean ± SE) in Participants Following Once Daily Dosing of Pemigatinib as Monotherapy in Study INCB 54828-101: A) C1D1, B) Steady State (C1D8/C1D14)



Note: Pemigatinib PK plasma samples were collected on C1D8 for the 1, 2, and 4 mg doses. PK plasma samples were collected on C1D14 for only 1 participant in the 6 mg dose group.

Table 9: Summary of pharmacokinetic parameters for pemigatinib as monotherapy (Parts 1 and 2) in Cycle 1 Day 1

Dose	Participant(s)	C_{max} (nM)	t_{max} (h)	AUC_{last} (h*nM)	AUC_{0-24} (h*nM)
1 mg	N = 1	25.3	1	190	191
2 mg	N = 1	13.6	5.92	68.8	--
4 mg	N = 1	109	2.02	1010	1010
6 mg	N = 4	64.6 ± 9.16 75.6 (14.2)	1.14 (1.00, 2.08)	641 ± 116 813 (18.1)	644 ± 115 816 (17.8)
9 mg	N = 21	139 ± 79.8 120 (60.6)	1.17 (0.500, 2.13)	1140 ± 498 1020 (60.5)	1150 ± 497 1020 (59.2)
13.5 mg	N = 69	196 ± 121 161 (73.7)	1.20 (0.400, 26.1)	1820 ± 1210 1540 (60.9)	1840 ± 1080 1610 (52.9)
20 mg	N = 19	300 ± 135 265 (59.6)	1.98 (0.500, 22.9)	2510 ± 935 2330 (45.7)	2850 ± 1050 2680 (37.4)

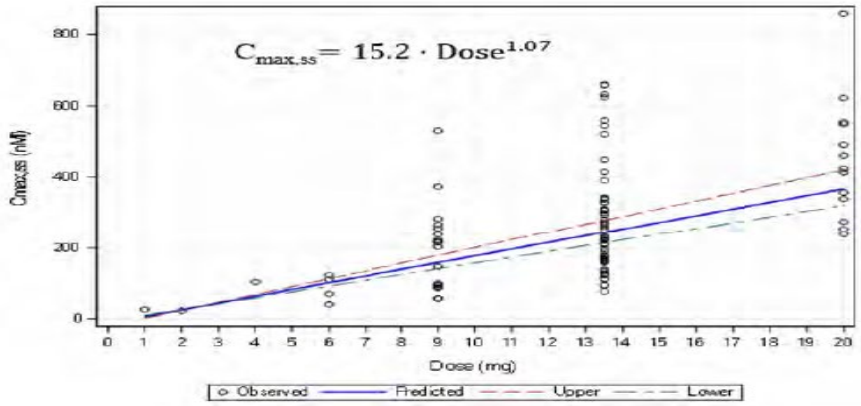
Table 10: Summary of PK parameters of pemigatinib as monotherapy (part 1 and 2) at C1D8/C1D14 in study INCB54828-101

Dose	Participant(s)	$C_{max,ss}$ (nM)	t_{max} (h)	$t_{½}$ (h)	$C_{min,ss}$ (nM)	$AUC_{ss,0-24}$ (h*nM)	CL_{ss}/F (L/h)	V_z/F (L)	Accumulation Ratio
1 mg	N = 1	26.2	1.07	10.9	3.24	208	9.86	156	1.09
2 mg	N = 1	22.9	3.98	18.1	7.87	322	12.8	334	1.64
4 mg	N = 1	103	2.02	30.4	23.9	1380	5.93	260	1.36
6 mg	N = 4	86.1 ± 38.0 78.8 (54.3)	1.58 (0.983, 23.7)	21.0 ± 22.8 14.5 (119)	30.0 ± 15.1 26.6 (64.3)	1080 ± 301 1050 (27.6)	12.0 ± 3.14 11.7 (27.6)	301 ± 241 244 (83.6)	1.67 ± 0.264 1.65 (16.8)
9 mg	N = 18	196 ± 123 162 (72.0)	1.00 (0.500, 6.10)	17.2 ± 9.70 14.7 (66.3)	49.9 ± 49.6 --	2180 ± 1630 1670 (95.1)	15.7 ± 17.7 11.1 (95.1)	246 ± 76.1 234 (33.6)	1.71 ± 0.534 1.64 (29.7)
13.5 mg	N = 57	271 ± 151 236 (56.4)	1.13 (0.500, 6.00)	17.4 ± 9.64 15.4 (51.6)	71.7 ± 56.7 56.8 (81.5)	3010 ± 1890 2620 (54.1)	11.9 ± 5.72 10.6 (54.1)	274 ± 165 235 (60.8)	1.69 ± 0.538 1.61 (33.7)
20 mg	N = 13	449 ± 172 421 (38.7)	1.12 (0.517, 5.90)	13.1 ± 6.01 12.1 (40.3)	104 ± 93.3 76.0 (98.1)	4350 ± 1480 4150 (32.1)	10.3 ± 3.01 9.88 (32.1)	180 ± 49.1 173 (29.2)	1.76 ± 0.476 1.70 (27.3)
P-values from a 1-factor ANOVA of log-transformed, dose-normalized data (factor = dose)									
Dose		0.632	--	--	--	0.943	--	--	--
Pairwise p-values from a 1-factor ANOVA of log-transformed, dose-normalized data (factor = dose)									
6 mg vs 9 mg		0.2841	--	--	--	0.8577	--	--	--
6 mg vs 13.5 mg		0.3042	--	--	--	0.7238	--	--	--
6 mg vs 20 mg		0.1259	--	--	--	0.5923	--	--	--
9 mg vs 13.5 mg		0.8214	--	--	--	0.7634	--	--	--
9 mg vs 20 mg		0.4315	--	--	--	0.5749	--	--	--
13.5 mg vs 20 mg		0.2595	--	--	--	0.6877	--	--	--

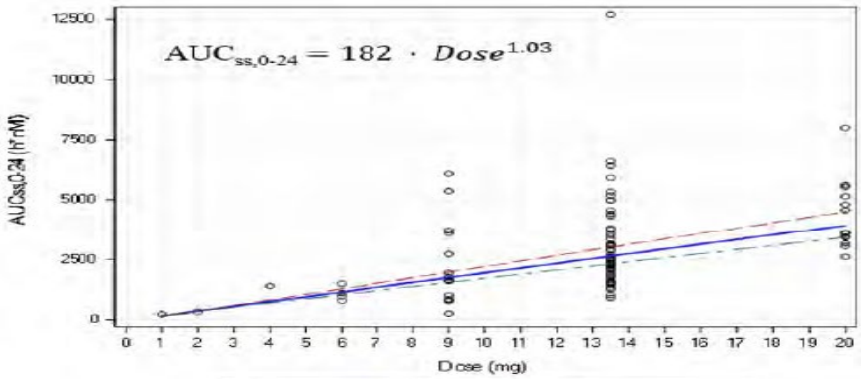
Based on data from patients with advanced malignances following once daily dosing of ascending doses of pemigatinib (study INCB 54828-101, part 1 and 2), the PKs of pemigatinib appears to increase in a dose proportional manner. Indeed, a dose proportionality analysis using C1D14 PK parameters ($C_{max,ss}$ and $AUC_{ss,0-24h}$) revealed no evident shift to dose proportionality over the dose range of 1 to 20 mg. The power-function regression analysis (figure **6**) produced dose-proportionality equations of $C_{max,ss} = 15.2 \times Dose^{1.07}$ ($p = 0.604$ for $\beta=1$) and $AUC_{ss,0-24} = 182 \times Dose^{1.03}$ ($p = 0.0.835$ for $\beta =1$). The exponent β, of the power function was not statistically significantly different from 1 for $C_{max,ss}$ or $AUC_{ss,0-24h}$. Furthermore, the provided ANOVA of dose-normalised PK parameters (Cmax,ss and AUCss,0-24) using overall test or pairwise comparisons between or across the dose range of 6 to 20 mg demonstrated that dose-normalised Cmax,ss or AUCss,0-24 was not statistically significantly different ($p > 0.05$). In addition, the dose proportionality was evaluated by comparing dose-adjusted least squares mean (LS mean) of $AUC_{ss,0-24}$ for the dose range of 6 to 20 mg. The differences in dose-adjusted AUCss,0-24 mean range from 5.71% to 18.9%.

Figure 4: Relationship of Dose and Pemigatinib Plasma Exposures in Individual Participants Receiving QD Dosing of Pemigatinib: A) Cmax,ss, B) AUCss,0-24h

A)



B)



Time dependency

Following once daily dosing of pemigatinib administrated on a 2 weeks on/ 1 week off therapy (= claimed intermittent dosing scheme) in patients with advanced malignances (study INCB 54828-101), the steady-state is predicted to be achieved after 4 to 5 days, based on the elimination half-life of 15 hours. Based on PK data collected at D14 postdose, the accumulation ratio (Racc) for pemigatinib following QD dosing was estimated at 1.6 based on AUCC1D14,0-24h/ AUCC1D1,0-24h. With the recommended dose of 13.5 mg QD, the geometric mean accumulation ratio was 1.61.

In absence of formal observed PK data due to PK sampling limitations in study INCB 54828-101, in which predose PK samples were only collected in Day 2, 8 and 14, data based on the population PK model (predicted AUCt, Cmin, Cmax) and the mean concentration time profile following administration of 13.5 mg QD on Days 2, 4, 6, 8 and 14 are provided. Based on these data and the elimination half-life of 15 hours it could be agreed that steady state is reached at approximately Day 4 after pemigatinib QD dosing.

Population Pharmacokinetic model

The applicant has performed a population PK modelling to describe the PK data of pemigatinib from three clinical studies. Presently the PopPK model is not considered suitable. The company has agreed to provide an updated PopPK model in the post authorisation setting by end of December 2021.

Special populations

Impaired hepatic function

A formal dedicated study (INCB 54828-107) investigating the effect of various degree of hepatic impairment on PKs of pemigatinib was performed.

Study INCB 54828-107 investigated the effect of moderate (n = 8 subjects Child-Pugh class B) and severe (n = 7 subjects Child-Pugh class C) hepatic impairment on PKs of pemigatinib after single 9-mg administration. PK results are summarised in the Tables below. Compared to healthy-matched participants, the geometric means pemigatinib AUCinf were 46% and 74% higher in the moderate and severe hepatic impaired groups, respectively.

Table 11: Comparison of pemigatinib PK parameters following administration of 9 mg pemigatinib tablets in participants with moderate hepatic impairment and healthy-matched participants

Hepatic Function	C_{max} (nM)	t_{max} (h)	$t_{½}$ (h)	AUC_{0-t} (nM*h)	$AUC_{0-\infty}$ (nM*h)	CL/F (L/h)	V_z/F (L)
Normal hepatic function (n = 8)	106 ± 44 98.3	1.00 (1.00, 2.00)	13.8 ± 4.2 13.3	1130 ± 607 1020	1170 ± 624 1060	19.4 ± 9.9 17.5	346 ± 93.8 336
Moderate hepatic impairment (n = 8)	114 ± 70 95.0	2.50 (0.500, 4.00)	18.9 ± 4.1 18.5	1560 ± 479 1480	1620 ± 514 1540	12.7 ± 5.0 12.0	337 ± 131 320
Geometric Mean Ratio and 90% Confidence Intervals							
Moderate hepatic impairment vs normal hepatic function	96.7% 59.4%-157%	--	--	146% 100%-213%	146% 100%-212%	--	--

Table 12: Comparison of pemigatinib PK parameters following administration of 9 mg pemigatinib tablets in participants with severe hepatic impairment and healthy-matched participants

Hepatic Function	C_{max} (nM)	t_{max} (h)	$t_{½}$ (h)	AUC_{0-t} (nM*h)	$AUC_{0-\infty}$ (nM*h)	CL/F (L/h)	V_z/F (L)
Normal hepatic function (n = 7)	107 ± 46 99.2	1.00 (1.00, 2.00)	14.0 ± 4.4 13.4	1200 ± 641 1070	1240 ± 658 1110	18.8 ± 10.7 16.7	336 ± 105 323
Severe hepatic impairment (n = 7)	95.3 ± 20.0 93.5	1.00 (1.00, 4.00)	23.8 ± 5.9 23.1	1870 ± 496 1810	2000 ± 568 1930	9.93 ± 3.01 9.56	322 ± 56.3 318
Geometric Mean Ratio and 90% Confidence Intervals							
Severe hepatic impairment vs normal hepatic function	94.2% 68.9%-129%	--	--	170% 114%-254%	174% 116%-261%	--	--

- Impaired renal function

A formal dedicated study (INCB 54828-108) investigating the effect of various degree of renal impairment on PKs of pemigatinib is ongoing.

Study INCB 54828-108 investigated the effect of severe renal impairment (n= 10 subjects with GFR <30 mL/min and not on hemodialysis) and End Stage Renal Disease (ESRD) (n= 9 with GFR <30 mL/min and on hemodialysis) on PKs of pemigatinib after single 9-mg administration. To note, subjects in ESRD group were administered a single dose of pemigatinib across 2 treatment periods before (Period 1) and after (Period 2) hemodialysis session.

PK results are summarised in the Tables below. Compared to healthy-matched participants, the geometric means pemigatinib AUCinf were 59% (90% CI = [95.4%, 264%] higher in the severe renal impaired group. Besides, compared to the reference healthy group, no meaningful difference in pemigatinib exposures AUCinf whether pemigatinib was administered before HD (GMR [90% CI] 76.8% [54.0%, 109%]) or after HD (GMR [90% CI] 91.3% [64.1%, 130%]) was observed in the ESRD group.

Table 13: Comparison of pemigatinib PK parameters following administration of 9 mg pemigatinib tablets in severe renal impairment and healthy-matched participants

Renal function	C_{max} (nM)	t_{max} (h)	$t_{½}$ (h)	AUC_{0-t} (nM*h)	$AUC_{0-\infty}$ (nM*h)	CL/F (L/h)	V_z/F (L)
Normal renal function (n=8)	113 ± 39.1 107	1.00 (1.00, 3.00)	14.1 ± 5.22 13.3	1100 ± 459 1030	1170 ± 541 1080	18.4 ± 7.13 17.1	332 ± 57.2 329
Severe renal impairment (n=8)	76.6 ± 35.9 69.0	1.51 (1.00, 6.00)	23.4 ± 11.0 21.4	1730 ± 951 1490	2120 ± 1450 1720	13.2 ± 8.84 10.8	358 ± 174 331
Geometric Mean Ratio and 90% Confidence Intervals							
Severe renal impairment vs normal renal function	64.6% 44.1% - 94.4%	--	--	145% 92.8% - 227%	159% 95.4% - 264%	--	--

Table 14: Comparison of pemigatinib PK parameters following administration of 9 mg pemigatinib tablets in ESRD and healthy-matched participants

Renal function	C_{max} (nM)	t_{max} (h)	$t_{½}$ (h)	AUC_{0-t} (nM*h)	$AUC_{0-\infty}$ (nM*h)	CL/F (L/h)	V_z/F (L)
Normal renal function (n=7)	107 ± 41.5 98.0	1.00 (1.00, 3.00)	15.3 ± 7.26 14.2	1160 ± 372 1120	1250 ± 416 1190	16.2 ± 5.22 15.5	328 ± 88.6 318
ESRD before HD (n=7)	80.8 ± 28.9 76.0	1.00 (1.00, 4.00)	14.5 ± 3.04 14.2	940 ± 404 873	983 ± 419 916	21.5 ± 8.06 20.2	436 ± 158 412
ESRD after HD (n=7)	93.3 ± 28.8 88.2	2.00 (1.00, 4.00)	17.4 ± 3.86 17.1	1100 ± 383 1030	1160 ± 424 1090	18.3 ± 8.15 17.0	427 ± 93.2 418
Geometric Mean Ratio and 90% Confidence Intervals							
ESRD before HD vs normal renal function	77.5% 51.2% - 118%	--	--	78.2% 55.3% - 111%	76.8% 54.0% - 109%	--	--
ESRD after HD vs normal renal function	90.0% 59.3% - 137%	--	--	92.3% 65.8% - 130%	91.3% 64.1% - 130%	--	--

- Gender, weight and elderly

No formal investigations with regard to gender, weight, elderly have been performed. Since no conclusions could be drawn from the PopPK analysis, the covariate effects on pemigatinib PK are considered unknown.

- Race

A formal study INCB 54828-102 investigating the PKs of pemigatinib in Japanese patients has been performed. PK results of this study indicated comparable systemic exposures of pemigatinib and PK parameters (CL/F, V/F and T1/2) at both C1D1 and C1D14 between Caucasian and Japanese populations. Therefore, the applicant considers that no dose adjustment between Caucasian and Japanese populations is deemed to be necessary. This conclusion could be endorsed.

The effect of race on the PKs of pemigatinib was also investigated using a PopPK approach. However, since no conclusions could be drawn from the PopPK analysis, the race effect on pemigatinib PK should be confirmed.

- Children

The safety and efficacy of pemigatinib in children and adolescents below 18 years of age have not been established. Pemigatinib is indicated in patients aged 18 years and older.

Pharmacokinetic interaction studies

In vitro data

Pemigatinib is a competitive or direct inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 mediated activity but with IC_{50} values >25 µM. Therefore, the potential for pemigatinib to cause clinically relevant drug-drug interactions via reversible inhibition of these CYPs is unlikely. There was no evidence of metabolism-dependent inhibition demonstrated for CYP2C9, CYP2C19, CYP2D6, or CYP3A4 from 1 to 25 µM.

Results from the sandwich-cultured human hepatocytes assay suggested that pemigatinib is not an *in vitro* inducer of CYP1A2 and CYP3A4 mRNA, but there is a potential for CYP2B6 induction by pemigatinib**.** Therefore, a warning regarding sensitive substrates of CYP2B6 has been reflected in section 4.5 of the SmPC .

Pemigatinib is a substrate for P-gp. The efflux ratio of pemigatinib was close to unity at three high concentrations tested (ratio of 1.5 at 1 µM, 0.89 at 10 µM and 0.64 at 30 µM) indicating the efflux transport is saturated at 1 µM of pemigatinib. Taking into account this saturation and the BCS class 2 of pemigatinib, P-gp inhibitors are not expected to affect pemigatinib exposure at clinically relevant concentrations. The calculated inhibition IC_{50} of digoxin transport by pemigatinib was 4.8 µM. This is lower than the worst expected concentration at the intestinal level, i.e. 11 µM (0.1 * dose / 250 mL), therefore pemigatinib inhibits P-gp. Clinically relevant DDI with substrates of this transporter such as dabigatran cannot be ruled out.

In MDCKII-BCRP cells the efflux mediated by BCRP was saturated at 30 µM (efflux ratio = 1.3). The efflux results indicate that pemigatinib is a substrate of BCRP. The net BCRP/control efflux ratio of prazosin (a prototype substrate of BCRP) decreased from 40 to 30 in the presence of 30 µM of pemigatinib, suggesting that pemigatinib is an inhibitor of BCRP (IC_{50} > 30 µM). Nonetheless, this is higher than the worst expected

concentration at the intestinal level, i.e. 11 µM (0.1 * dose / 250 mL), therefore clinically relevant interactions related to BCRP inhibition by pemigatinib are unlikely.

In vitro experiments were conducted to evaluate the inhibitory potential of pemigatinib against human uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and efflux transporters MATE1 and MATE2K. Summary PK parameters are given in the table below:

Table 15: IC_{50} values for inhibition of human transporters by pemigatinib

Transporter	Pemigatinib concentration	Cell line	Probe substrate (concentration)	Positive control (concentration)	IC_{50} (µM)	Report Number
					Pemigatinib	
P-gp	0-50 µM	Caco-2	Digoxin (5 µM)	Cyclosporin A (5 µM)	**4.8**	DMB-14.61.1
BCRP	0-30 µM	MDCKII-BCRP	Prazosin (1 µM)	Ko143 (3 µM)	> **30**	DMB-14.61.1
OATP1B1	0-33 µM	CHO-hOATP1B1	estrone 3-sulfate) (0.1 µM)	Cerivastatin (100 µM)	**NC**	DMB-14.62.1
OATP1B3	0-33 µM	CHO-hOATP1B3	Estradiol-17β-glucuronide (0.2 µM)	Cyclosporin A (10 µM)	**3.0**	DMB-14.62.1
OCT2	0-33 µM	CHO-hOCT2	metformin (10 µM)	verapamil (100 µM)	**0.075**	DMB-14.62.1
OAT1	0-33 µM	CHO-hOAT1	*p*-aminohippuric acid (1 µM)	benzbromarone (200 µM)	**NC**	DMB-14.62.1
OAT3	0-33 µM	Flp-In™-293-hOAT3	Estrone-3-sulfate (0.24 µM)	Probenecid (100 µM)	> **33**	DMB-14.62.1
MATE1	0-33.3 µM	MDCKII-MATE1-Fin	Metformin (10 µM)	Pyrimethamine (1 µM)	**1.1**	DMB-18.141.1
MATE2K	0-33.3 µM	MDCKII-MATE2-K-Fin	Metformin (10 µM)	Pyrimethamine (10 µM)	**15.3**	DMB-18.141.1

NC: not calculated

Based on this table,

- Pemigatinib is an inhibitor of OATP1B3 (25*Cinlet,u of 7.4 µM > IC_{50}).
- With a 50*Cmax,ss,u of 2.8 µM > IC_{50} (Observed Cmax,ss of 402 nM, fu of 11.2 % and blood/plasma of 0.8), pemigatinib is an inhibitor of OCT2 and MATE1. Clinically relevant interactions with sensitive substrates (e.g metformin) cannot be ruled out.

In silico

A PBPK model was built in order to predict drug-drug interactions (study DMB-19.25.1).

The pemigatinib PBPK model-predicted AUC ratio of 1.98 (90% CI: 1.91, 2.05) and C_{max} ratio of 1.22 (90% CI: 1.20, 1.24) were similar to the observed AUC ratio of 1.88 (90% CI: 1.75, 2.03) and C_{max} ratio of 1.17 (90% CI: 1.07, 1.29) for itraconazole DDI. The predicted geometric mean AUC ratios and C_{max} ratios were within the 90% CI of the observed data.

Underprediction was observed for rifampin DDI. The model-predicted AUC ratio of 0.323 (90% CI: 0.299, 0.349) and C_{max} ratio of 0.604 (90% CI: 0.572, 0.638) were approximately 1.5 to 2-fold higher compared to the observed AUC ratio of 0.149 (90% CI: 0.139, 0.161) and C_{max} ratio of 0.380 (90% CI: 0.332, 0.425) for rifampin DDI. Co-administration of strong and moderate CYP3A4 inducers should be avoided and no dose adjustment is required with co-administration of pemigatinib and weak CYP3A4 inducers.

As highlighted in EU Guideline on modeling and simulation, PBPK is not sufficiently robust to adequately predict the pharmacokinetic profile of DDI driven by induction. Therefore, only a dedicated clinical study will ensure appropriate estimation of the PK profile of a substrate when combined with a perpetrator. As regards pemigatinib, see results from the clinical study in the *in vivo* part thereafter.

As regards PK predictions related to transporters, the lack of clinical studies with substrates of P-gp, OCT2 and MATE1 cannot allow any conclusion to be drawn since the model needs these data to be built.

In vivo studies

Two drug-drug interaction studies on impact on pemigatinib as victim were performed by the applicant.

Study INCB 54428-104 used itraconazole as inhibitor and rifampicin as inducer of pemigatinib metabolism. The study design was acceptable and the results show an 88% increase of AUC of pemigatinib with itraconazole and an 85% decrease of the AUC of pemigatinib by rifampicin. Concurrent use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) should be avoided during treatment with pemigatinib.

Study INCB 54428-106 investigated the impact of gastric pH-modifying agents on pemigatinib exposure. With esomeprazole, a 35% decrease of Cmax and an 8% decrease of AUC were observed in healthy subjects. With ranitidine, changes were negligible (-2% and +3%, respectively). Notable, co-administration of a proton pump inhibitor (esomeprazole) did not result in a clinically important change in pemigatinib exposure in study INCB 54828-101. However, in more than one third of patients given PPIs, a significant reduction of the exposure of pemigatinib was observed. Thus, PPIs should be avoided in patients receiving pemigatinib.

2.4.3. Pharmacodynamics

Mechanism of action

Pemigatinib is a kinase inhibitor of FGFR1, 2 and 3 which inhibits FGFR phosphorylation and signalling and decreases cell viability in cells expressing FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements. FGFR2 fusions/rearrangements are strong oncogenic drivers and are the

most common FGFR alteration occurring, almost exclusively, in 10-16 % of intrahepatic cholangiocarcinoma (CCA).

Primary and Secondary pharmacology

Primary pharmacology

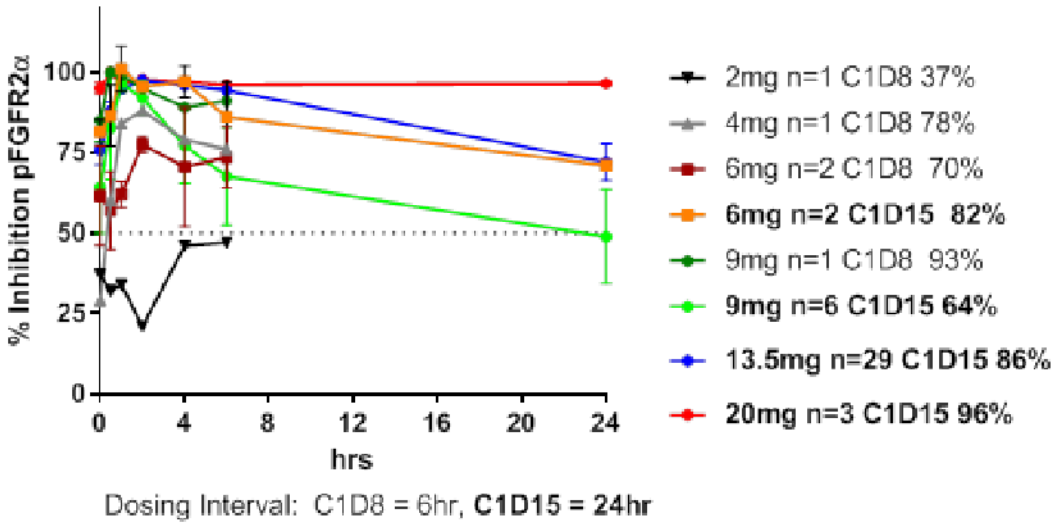
Pemigatinib is a potent selective inhibitor of FGFR1, FGFR2, and FGFR3, and is proposed for the treatment of advanced malignancies with FGFR alterations with activated FGFR pathway. The potency of pemigatinib is expected to be the same for the FGFR2 rearrangements based on the rationale that the kinase domain remains unaltered.

In enzymatic assays, pemigatinib potently inhibited the kinase activity of FGFR1, FGFR2, and FGFR3 with IC_{50} values ranging from 0.39 to 1.2 nM. It had weaker inhibitory potency against FGFR4 (30 nM) and was selective against VEGFR2 (59- to 182-fold for FGFR3 and FGFR1, respectively).

The phosphorylation of FGFR2α was used to measure levels of FGFR activation/inhibition by the addition of exogenous KATOIII cells, a gastric cell line with amplified FGFR2, utilising a commercially available solid phase sandwich ELISA. Within the INCB 54828-101 dose-escalation study, in participants with advanced malignancies, pFGFR2α was measured on C1D1 and C1D14 (with the exception of 5 participants administered study drug at C1D1 and C1D8) at various time points.

In the monotherapy cohorts, the figure below demonstrates dose-dependent average percentage pFGFR2α inhibition from 2 mg cohort (n = 1) at 37% to 96% at 20 mg (n = 3) [13.5 mg (N = 29)].

Figure 5: Inhibition of FGFR2α phosphorylation at Steady State (C1D14, 0-24 Hour) in INCB 54828-101 Monotherapy Cohorts (Mean ± SEM)

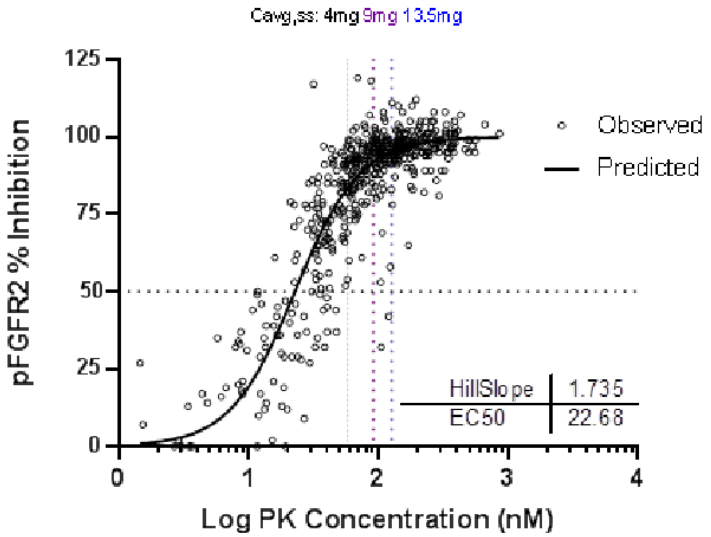


Note: The 2 mg and 4 mg steady state collected on C1D8 to 6 hours; 6 mg-20 mg steady state collected on C1D14.

Consistently, the observed inhibition of pFGFR2 from participants collected at trough was 37% at the 2 mg QD dose and 96% after the 20 mg QD dose.

PK/PD analysis of preliminary PK INCB054828 concentrations in plasma and pFGFR2α inhibition from participants in all cohorts (including combination therapy not further discussed here) calculated an IC_{50} of 24 nM, consistent with the preclinical *in vivo* IC_{50} of 23 nM:

Figure 6: Pharmacokinetic/Target Coverage Analysis - pemigatinib (nM) vs. % Inhibition pFGFR2α (69 Participants from all cohorts in INCB 54828-101)



Note: Preliminary PK concentration data to date for this study 12/2018; 1 participant C1D1 only.

Inhibition of FGFR signalling led to a compensatory increase in endocrine FGF (FGF19, FGF21, and FGF23) levels. These compensatory increases were used as markers of FGFR inhibitory activity of pemigatinib. FGF23 was used as a pre-specified marker for FGFR activity. C1D1 and C1D15 samples were assayed using a commercially available FGF23 assay from MSD.

There was a statistically significant increase in FGF23 levels across all dose groups, with an average 3.2-fold change at 13.5 mg. Differences between the 6, 9, and 13.5 mg cohorts were not statistically significant (median change 2.7-fold).

Olink biomarker analysis found that 5 analytes (FGF23, FGF21, chordin-like 2 [CHRDL2], carbonic anhydrase 6 [CA6], and desmoglein 4 [DSG4]) were differentially expressed based on an absolute fold change > 1.5-fold in plasma samples from C1D15 vs. C1D1.
Two assays were present in the panel for FGF23, with both meeting this cut-off for statistical significance. The mean change for FGF23 was a ~4-fold upregulation of FGF23 across all dose groups and cohorts. FGF21 was also upregulated, although to a lesser extent than FGF23.

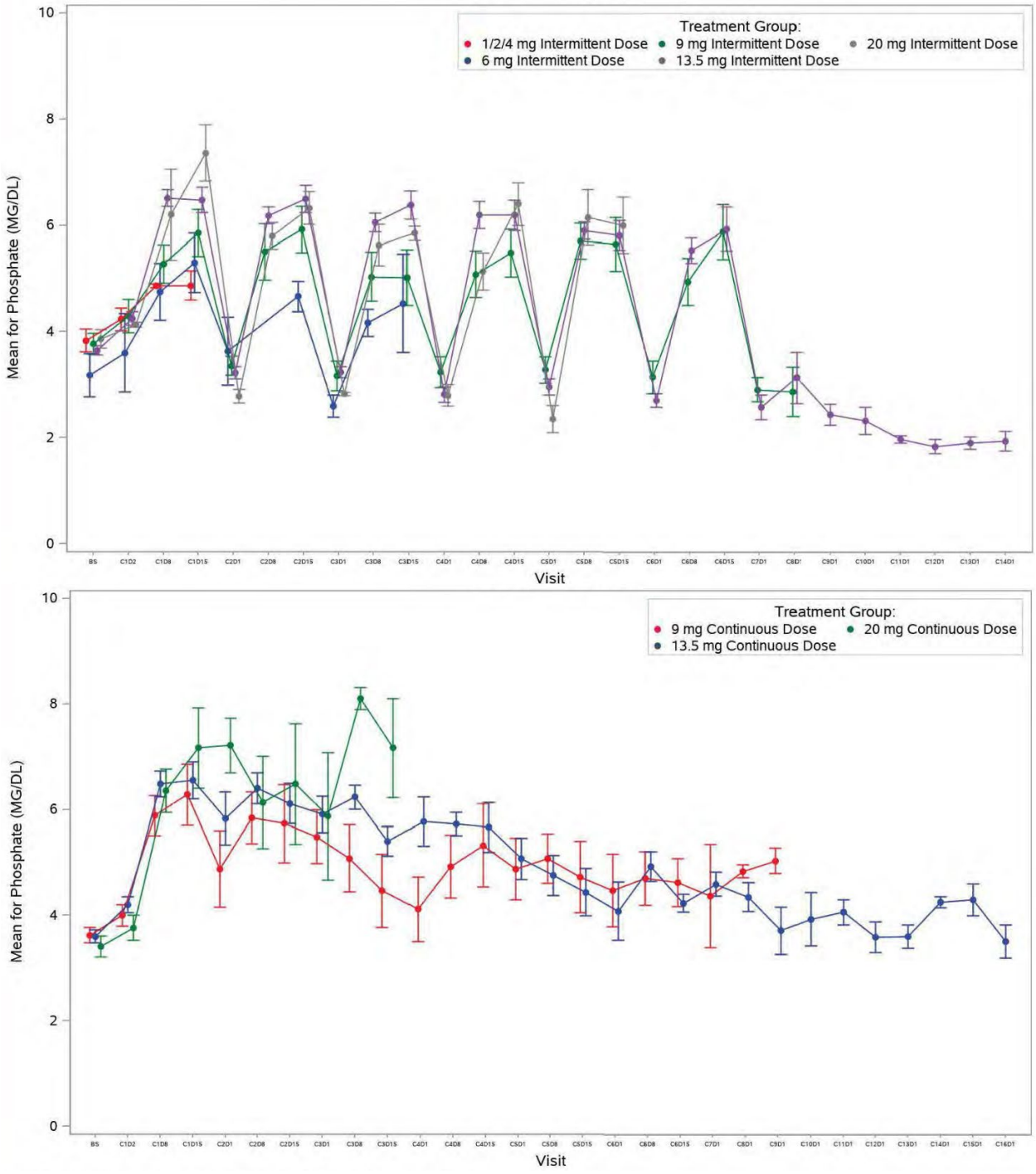
It is unknown whether these markers return to baseline levels after the 1-week pemigatinib drug holiday as these samples were not evaluated.

Secondary pharmacology

Hyperphosphatemia is an expected on-target pharmacological effect of FGFR inhibition. The incidence of hyperphosphatemia, defined as any post-baseline phosphate level exceeding 5.5 mg/dL, has been observed

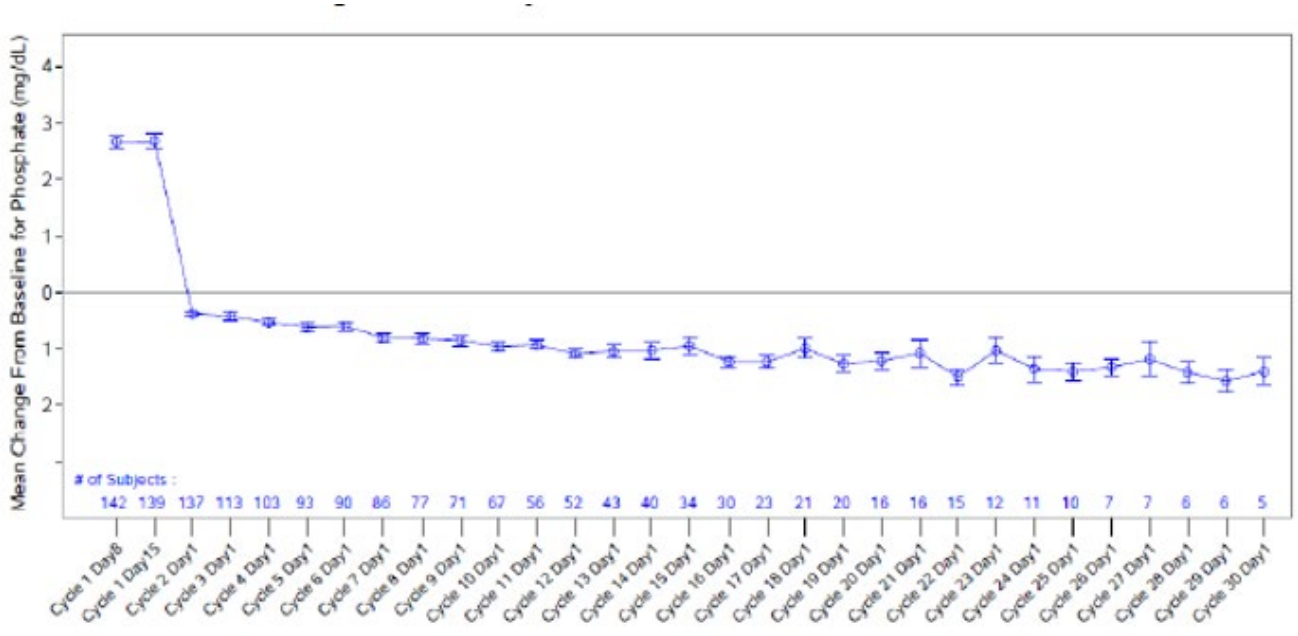
in the majority of participants treated with pemigatinib and appears to be dose-dependent as demonstrated in Parts 1 and 2 of Study INCB 54828-101.

Figure 7*:* Mean (± SE) Serum phosphate over time under QD intermittent (upper) and continuous (lower) pemigatinib (INCB 54828-101 Part 1 and 2)



In Study INCB 54828-202, the time course of trough serum phosphate following treatment with pemigatinib shows a steady downward trend:

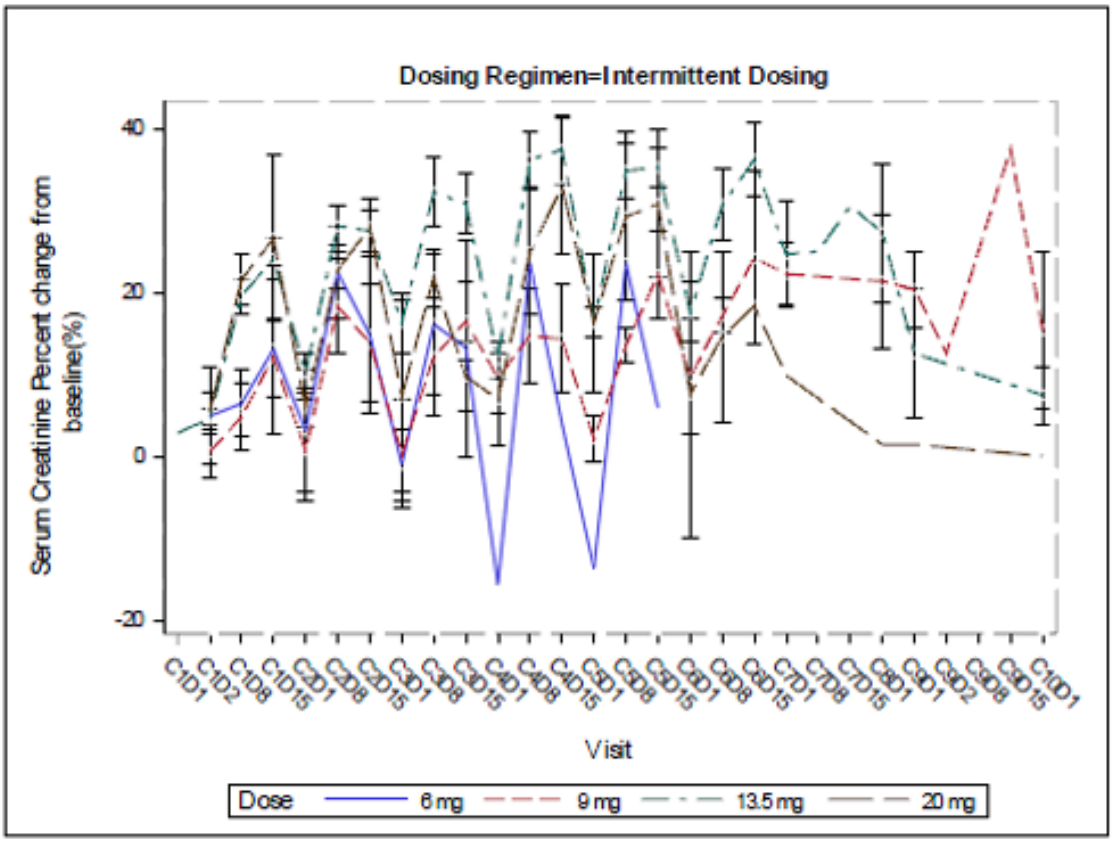
Figure 8: Mean (±SE) change from baseline in serum phosphate levels over time in participants in study INCB 54828-202

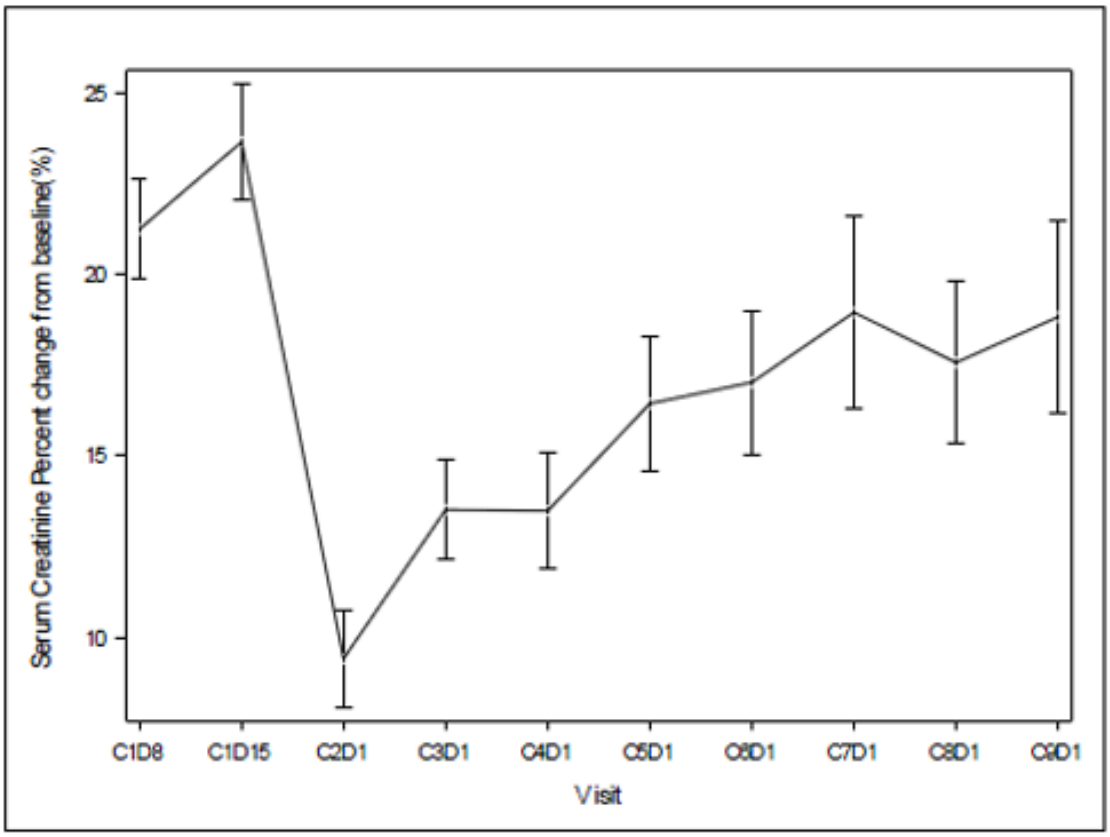


Based on the data of Study INCB 54828-101, a basic E_{max} model was developed to demonstrate the relationship between pemigatinib exposure ($AUC_{ss,0-24}$) and the highest observed serum phosphate concentration following QD dosing of pemigatinib as monotherapy. This was further developed with data from studies 102 and 202, see ER analyses below.

The serum creatinine concentration increased and reached steady state approximately in C1D8 after once daily dosing of pemigatinib and the concentration decreased during the drug holiday. Trough levels steadily increased during treatment.

Figure 9: Observed serum creatinine concentration (mean ± SE) under pemigatinib (study 101 upper, study 202 lower)





Cardiac safety

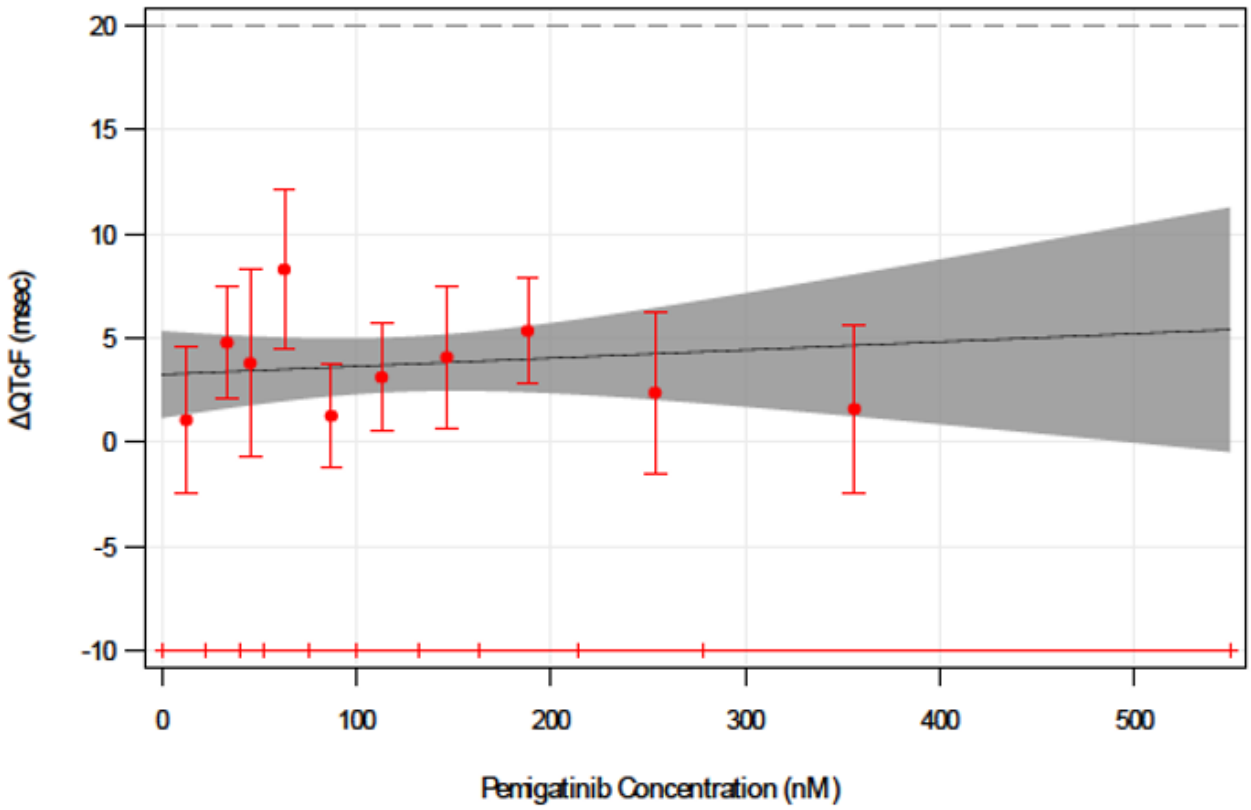
A cardiac safety analysis was performed using 12-lead ECG data from 116 participants treated with pemigatinib at doses of 1 to 20 mg QD in Study INCB 54828-101. Timed 12-lead ECGs were performed within 15 minutes prior to PK blood draw at the corresponding time point and analysed at the central ECG laboratory using a semi-automated technique.

In the concentration-QTc analysis, plasma concentration data and time-matched triplicate ECGs collected from participants in Study INCB 54828-101 who received pemigatinib as monotherapy were used. The primary endpoint was the baseline adjusted QTcF (ΔQTcF). The relationship between pemigatinib plasma concentrations and ΔQTcF was investigated using a linear mixed effects model.

The estimated slope of the C-QTcF relationship was shallow and not statistically significant: 0.00391 msec per nM (90% CI: -0.01244, 0.02026). Using this C-QTcF model, the QT effect (ΔQTcF) was predicted to be 4.18 msec (90% CI: 2.13, 6.24) at the 13.5 mg QD dose level (observed Cmax,ss = 235 nM [56.7% CV]) and 4.91 msec (90% CI: 0.60 to 9.22) at the highest dose level studied (20 mg QD, observed $C_{max,ss}$ = 421 nM [38.7% CV]).

The upper bound of the 2-sided 90% CI around the effect on QTc at 13.5 mg was less than 10 ms, which did not suggest a clinically relevant QTc prolongation at the proposed therapeutic dose.

Figure 10: Model Predicted ΔQTcF (mean and 90% CI) Overlaid With Observed Mean ΔQTcF (mean and 90% CI) Across Deciles of Pemigatinib Plasma Concentrations



PK/PD modelling

Two modelling and simulation reports have been provided: one PK and exposure-response analysis and one PBPK modelling report on drug-drug interactions. Several analyses (efficacy and safety) were performed (data not shown), however, as the PopPK model is presently not considered adequate, no conclusion from these analyses can be made. The applicant has committed to provide an updated version in the post authorisation setting.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The clinical pharmacology programme supporting this application is based on results from six clinical studies, as part of Phase 1 and 2 studies. The PKs of pemigatinib was evaluated in healthy volunteer studies after single oral administration, including a 14C-labeled mass balance study (INCB 54828-105), drug interaction study with a CYP 3A4 inhibitor or inducer (INCB 54828-104), drug interaction study with a proton pump inhibitor or a H2-receptor antagonist (INCB 54828-106). Additionally, PKs of pemigatinib following once daily dosing of pemigatinib administrated on a 2 weeks on/ 1 week off therapy (= claimed intermittent dosing scheme) are available from cancer patients in phase 2 studies (INCB 54828-101, INCB 54828-102 and INCB 54828-202).

In addition, the PKs of pemigatinib were characterised in special populations with hepatic dysfunction (INCB 54828-107) and renal impairment (INCB 54828-108) and final data were submitted during the procedure.

Overall, PKs of pemigatinib has been sufficiently characterised in healthy subjects and in patients with advanced malignancies based on the formal phase 1 and 2 studies (NCA approach with rich PK samples).

Overall, PK data suggest an almost complete absorption of pemigatinib and an extensive distribution into the extra vascular tissues. The qualitative metabolite profile of pemigatinib in human was similar to those in preclinical species, thus no human specific metabolites were identified and the data indicate that the biliary clearance rather than the renal route is the major elimination route for pemigatinib

Overall, the dose proportionality analysis demonstrated that the mean pemigatinib $C_{max,ss}$ and $AUC_{ss,0-24}$ increased linearly proportional to the dose from 1 to 20 mg. This finding is not completely endorsed as data for dose levels of 1, 2 and 4 mg were collected only from very few patients (n=1 for each level) and thus could not be considered as reliable. Conclusively, it is agreed that PKs (AUCss and C_{maxss}) of pemigatinib appear to increase in a dose proportional manner following multiple dosing within the therapeutic dose range of 6 to 13.5 mg.

PK data from patients have been pooled and analysed by a Pop-PK. Of note, only sparse PK data were available in patients with cholangiocarcinoma with FGFR2 rearrangement (being the target population for the current submission). Presently the developed PopPK model is not considered adequate, and so are consequent conclusion drawn from the ER analysis, since several methodological problems were identified (data not shown). This hampers particularly the need (or not) of dose adaptation in the female patients which appear overexposed compare to male patients. Nevertheless, the applicant was recommended to submit updates of the PopPK model and ER analyses.

Based on results from study INCB 54828-107, no dose adjustment is proposed for the patients with mild and moderate hepatic impairment. For the severe hepatic impairment; recommendation is given that pemigatinib doses should be reduced from 13.5 mg to 9 mg and from 9 mg to 4.5 mg. These is agreed and has been properly included in the SmPC.

Based on these results, no dose adjustment is proposed for ESRD patients undergoing haemodialysis. For the severe renal impaired group, recommendation is given that pemigatinib doses should be reduced from 13.5 mg to 9 mg and from 9 mg to 4.5 mg. For patients with mild and moderate renal impairment, no dose adjustment is recommended as the over-exposure awaited for both groups is expected to be lower than that observed with severe impaired group. These proposals are acceptable and adequately included in the SmPC.

Interactions

Based on current *in vitro* results, pemigatinib seems to induce only CYP2B6 in the study performed to assess induction potential on CYP3A4 and CYP1A2. *In vitro*, pemigatinib is also an inhibitor of the efflux transporters P-gp, BCRP and MATE-1 and of the uptake transporter OCT1B3 and OCT2, therefore clinically relevant concentrations cannot be ruled out for sensitive substrates.

In the clinical setting, pemigatinib was only investigated as victim.

Strong CYP3A4 inhibitors

A strong CYP3A4 inhibitor (itraconazole 200 mg once daily) increased pemigatinib AUC geometric mean by 88 % (90 % CI of 75 %, 103 %), which may increase the incidence and severity of adverse reactions with pemigatinib. Patients who are taking 13.5 mg pemigatinib once daily should have their dose reduced to 9 mg

once daily and patients who are taking 9 mg pemigatinib once daily should have their dose reduced to 4.5 mg once daily.

CYP3A4 inducers

A strong CYP3A4 inducer (rifampin 600 mg once daily) decreased pemigatinib AUC geometric mean by 85 % (90 % CI of 84 %, 86 %), which may decrease the efficacy of pemigatinib. Concurrent use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) should be avoided during treatment with pemigatinib. Concomitant use of pemigatinib with St John's wort is contra-indicated. If needed, other enzyme inducers (e.g. efavirenz) should be used under close surveillance.

Proton pump inhibitors (PPI)

Pemigatinib geometric mean ratios (90 % CI) for Cmax and AUC were 65.3 % (54.7, 78.0) and 92.1 % (88.6, 95.8), respectively, when co-administered in healthy subjects with esomeprazole relative to pemigatinib alone. Co-administration of esomeprazole did not result in a clinically important change in pemigatinib exposure. However, in more than one third of patients given PPIs, a significant reduction of the exposure of pemigatinib was observed.

An ad-hoc efficacy analysis from study FIGHT-302 (Annex II condition) on patients with PPIs versus without will be performed, to assess if there is any impact on survival due to reduced bioavailability of pemigatinib secondary to increased stomach pH due to PPI use, once data is available. In this study, pharmacokinetic samples will be obtained for participants randomised to the pemigatinib treatment group. Until further data is available, concomitant use of PPI should be avoided (see SmPC section 4.4 and 4.5).

PBPK models need further validation and qualification. Besides, PBPK is not considered as robust enough yet to assess impact of inducers on pemigatinib PK profile or the effect of pemigatinib on transporters (data not shown). The applicant was recommended to provide an updated PBPK model analysis as soon as available.

Pharmacodynamics

Overall, the rationale for investigating pemigatinib's inhibitory effect on kinase activity of FGFRs in cholangiocarcinoma patients with FGFR2 rearrangements is passably outlined.

Pemigatinib is considered to be a competitive inhibitor of ATP.

With regard to main study, CCA patients were grouped into 3 cohorts, Cohort A is the representative cohort for primary and key secondary efficacy endpoints:

- Cohort A: FGFR2 translocations with a documented fusion partner in central laboratory report
- Cohort B: other FGF/FGFR alterations
- Cohort C (US only): negative for FGF/FGFR alterations.

Although it seems from the provided literature that in case a CCA tumour has alterations in FGFR this is mostly restricted to FGFR2, it was considered insufficiently justified why only FGFR2 but not the other two (FGFR1 and FGFR3) should be inhibited in patients in view of the comparable low-nanomolar IC_{50} at all 3 subtypes; why only FGFR2 with alterations/fusions should be inhibited but not "unmutated" FGFRs, based on the comparable IC_{50} at native and oncogenic FGFR subtypes; and why the main efficacy was proposed for cohort A. This was explained by the applicant that pemigatinib was developed as an inhibitor acting specific against FGFR2 while binding on FGFR1 and FGFR3 was called negligible. This assumption was based on the

fact that deletion of the C-terminus exon of FGFR2 results in decreased receptor internalisation/degradation, increased receptor auto-phosphorylation/activation, sustained activation of FRS2 and resultant constitutive FGFR2 signalling and may therefore be specific for the FGFR2 receptor as an oncogenic driver. Indeed, this would explain the selectivity of pemigatinib inhibitory effects at for FGFR2, although the IC_{50} values demonstrated similar binding capacity also on FGFR1 and FGFR3 native and unmutated.

Biomarker data were presented from additional analyses of PD samples from C2D1. These new data suggest that the upregulation of certain markers such as FGF-23, FGF-21 at end of 14-days treatment decreases during the 1-week treatment pause. It was discussed that the continuing FGF-23 elevation after drug pause may be contributing to the continuous hypophosphataemia.

In this regard, despite only very few data from cohort C patients, it can be deduced that the compensatory upregulation of FGF-23 is also present in CCA patients lacking the target FGFR2 rearrangements and fusions. This means that such patients suffer from adverse effects of pemigatinib like hyperphosphataemia while obviously lacking clinical benefit. This patient population should therefore not be treated with pemigatinib.

Moreover, the NGS assay of FGFR2 gene biomarkers used for patient selection in study INCB 54828-202 was questioned, e.g. on the two different versions (315 genes vs 395 genes) utilised. The CTA was based on the T7 bait-set and contained 395 genes. Patients entering the study with an existing FoundationOne report may have used an earlier version of the panel containing 315 genes. In either case, the FGFR2 content was the same independent of which assay version was used. Furthermore, as participants carrying FGFR2 rearrangements (cohort A) showed confirmed tumour responses whereas patients with other or no FGF/FGFR alterations did not (cohorts B and C), this could be critical for the assessment of the clinical validity of the biomarker. Nevertheless, the lack of responses in this marker negative population could be expected since only FGFR2 fusions or rearrangements CCA patients can respond to pemigatinib from the mode of action.

Several exposure-response analyses (efficacy and safety) were performed, however as the PopPK model is presently not considered adequate, no conclusion from these analyses can be made. The applicant was recommended to provide an updated version in the post authorisation setting.

2.4.5. Conclusions on clinical pharmacology

Overall, the PKs of pemigatinib has been sufficiently characterised in healthy subjects and in the target patients based on formal phase 1 and 2 studies.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

Issues remaining with regards to the population PK analysis for pemigatinib will be addressed with an update by the applicant in the post authorisation setting through a recommendation for an updated PK/PD modelling analysis.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The pemigatinib dosing regimen (recommended Part 2 doses (RP2D) 13.5 mg QD on a 2-weeks-on/1-week-off schedule) for the pivotal study (FIGHT-202), was selected based on the data observed in the first-in-human study of pemigatinib, study INCB 54828-101.

Study INCB 54828-101 was an open-label, dose-escalation and expansion study of pemigatinib administered alone or in combination with another cancer therapy in participants with advanced malignancies. This first-in-human study evaluated the safety and tolerability, PK, and pharmacodynamics and defined the RP2D(s) of pemigatinib. Preliminary efficacy (antitumour activity assessed using disease-specific techniques) was also being evaluated.

Eligible participants received escalating doses of pemigatinib from 1 to 20 mg administered on an intermittent schedule or pemigatinib 9 to 20 mg administered continuously. Therapies to be administered in combination with pemigatinib included gemcitabine and cisplatin, docetaxel, pembrolizumab, trastuzumab, and INCMGA00012.

As of the data cutoff date (19 FEB 2019), 160 participants were enrolled: 116 received pemigatinib monotherapy (45 men/71 women; median age, 57.5 years). Among the 116 participants on pemigatinib monotherapy, 16 had cholangiocarcinoma, 8 of whom had FGFR2-rearranged cholangiocarcinoma. In Study INCB 54828-101, a best overall response of PR was observed in 3 participants of 8 with FGFR2-rearranged cholangiocarcinoma (ORR based on investigator-assessed was 37.5%): 1 participant initially treated with pemigatinib 9 mg QD on an intermittent schedule, 1 participant treated with pemigatinib 13.5 mg QD on an intermittent schedule, and 1 participant treated with pemigatinib 13.5 mg QD on a continuous schedule. Durations of response were 3.32, 7.29, and 11.30 months respectively. All three participants with a BOR of PR eventually discontinued pemigatinib treatment due to disease progression. A total of five participants had a BOR of SD. No additional efficacy data were analysed.

No participant on pemigatinib monotherapy had a DLT, and an MTD of pemigatinib was not identified. Among participants on pemigatinib monotherapy, the most common TEAE was hyperphosphatemia (69.0%), which was managed with a low-phosphate diet, phosphate-lowering medication, or pemigatinib dose modification. Other common events (> 30%) included fatigue (39.7%), dry mouth (38.8%), alopecia and stomatitis (31.9% each), and diarrhea (30.2%). Sixty-six participants (56.9%) had ≥ Grade 3 TEAEs, the most frequent of which were fatigue (8.6%); hyponatremia and pneumonia (6.9% each); and anaemia, hypophosphatemia, and stomatitis (5.2% each). Forty-seven participants (40.5%) had serious TEAEs, the most frequent of which were events of pneumonia (6.9%). In addition, preliminary safety data from combination therapy cohorts available at the time of the data cutoff date suggest no unexpected toxicities based on the safety profile of pemigatinib and that of each of the combination agents.

According to safety, tolerability, PK, and pharmacodynamic data of the study INCB 54828-101, pemigatinib 13.5 mg was selected as the RP2D for monotherapy.

Study INCB 54828-102 was an open-label, dose-escalation and expansion study of pemigatinib in Japanese participants with advanced solid tumours. This study evaluated the safety and tolerability, PK, and pharmacodynamics of pemigatinib in a Japanese population. The starting dose was 9 mg and eligible

participants receive escalating doses of pemigatinib on an intermittent or continuous schedule (dose expansion only).

As of the data cutoff date (18 JAN 2019), 25 participants have been enrolled (16 men/9 women; median age, 63.0 years). Among the 25 participants treated with pemigatinib, 3 had cholangiocarcinoma, one of whom had FGFR2-rearranged cholangiocarcinoma. The single participant with FGFR2-rearranged cholangiocarcinoma in this study received pemigatinib 13.5 mg QD on an intermittent schedule and had an investigator-assessed best overall response of stable disease with a PFS duration of 4.01 months.

The most common TEAEs were hyperphosphatemia (76.0%), dysgeusia (36.0%), and alopecia (32.0%). Hyperphosphatemia was managed with diet, phosphate-lowering medication, or dose modification. The MTD had not been reached at the time of the data cutoff date for this study. Eleven participants (44.0%) had ≥ Grade 3 TEAEs, the most frequent of which were anemia, cholangitis, and decreased appetite in 2 participants (8.0%) each, and 10 participants (40.0%) had serious TEAEs, the most frequent of which was cholangitis in two participants (8.0%). Pemigatinib 13.5 mg QD was selected as the recommended starting dose for Part 2 of the study.

The maximum dose administered in this study as of the data cutoff date was 13.5 mg QD on an intermittent schedule in Japanese participants with advanced solid tumours.

All nine participants with FGFR2-rearranged cholangiocarcinoma enrolled across both studies (INCB 54828-101 and INCB 54828-102) had reductions from baseline in target lesion diameters ranging from -8.0% to -49.5%.

2.5.2. Main study

Main study

INCB 54828-202

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy (FIGHT-202)

Methods

The study FIGHT-202 is an ongoing, prospective, open-label, single-arm, multinational study evaluating the efficacy and safety of pemigatinib in participants with advanced/metastatic or surgically unresectable cholangiocarcinoma who have progressed on at least 1 line of prior systemic therapy.

Participants were assigned to cohorts based on tumour FGF/FGFR status from the central genomics laboratory. Cohort A includes participants with FGFR2 rearrangement or fusions. The term "translocation" was initially used to describe the genetic alterations in Cohort A. With increased understanding of FGFR2 genetic alterations in cholangiocarcinoma, the terminology has evolved to "rearrangements or fusions" to more precisely describe these genetic alterations. Cohort B includes participants with other FGF/FGFR alterations, and Cohort C includes participants who are negative for FGF/FGFR alterations.

Study Participants

Key inclusion criteria

1. Men and women, aged 18 or older.
2. Histologically or cytologically confirmed advanced/metastatic or surgically unresectable cholangiocarcinoma. Subjects were assigned to 1 of 3 cohorts:
    a. Cohort A: FGFR2 translocations with a documented fusion partner in central laboratory report
    b. Cohort B: other FGF/FGFR alterations.
    c. Cohort C (US only): negative for FGF/FGFR alterations.
3. Radiographically measurable disease per RECIST v1.1.
4. Documentation of FGF/FGFR gene alteration status.
5. Documented disease progression after at least 1 line of prior systemic therapy.
6. Archival tumour specimen (formalin fixed paraffin-embedded [FFPE] tumour block or approximately 15 slides) or willingness to undergo a pretreatment tumour biopsy to provide a tumour block or unstained slides. Archival tumour biopsies are acceptable and should be no more than 2 years old (preferably < 1 year old and, if possible, collected since the completion of the last treatment); subjects with a sequencing report from the central genomic laboratory within approximately 2 years of screening are exempt from the need for tumour biopsy, but a tumour sample should be provided to the sponsor if available.
7. Life expectancy ≥ 12 weeks.
8. ECOG performance status 0 to 2.
9. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea).
    b. Woman of childbearing potential who has a negative pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed. A follow-up pregnancy test will be performed at EOT visit.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after last day of treatment (1 sperm cycle). Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.

Previous therapies may include chemotherapeutic agents, immunotherapies, with or without radiotherapy. Subjects receiving radiotherapy to target lesion(s) must show progression of target lesion before entry into the study.

Subject eligibility could be based on local genomic testing results, if available. Confirmatory testing through the central genomics laboratory was expected to be performed on all subjects.

Subjects enrolled based on a local sequencing report were planned to be assigned to a cohort based on the local results. However, final cohort assignment for statistical analysis of primary and secondary endpoints were expected to be based on the central genomics testing results.

Key exclusion criteria

1. Prior receipt of selective FGFR inhibitor.
2. Untreated brain or central nervous system (CNS) metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with previously treated and clinically stable brain/CNS metastases and who are off all corticosteroids for ≥ 4 weeks are eligible.
3. Have abnormal laboratory parameters:
    a. Total bilirubin ≥ 1.5 × upper limit of normal (ULN; ≥ 2.5 × ULN if Gilbert syndrome or disease involving liver).
    b. AST and ALT > 2.5 × ULN (AST and ALT > 5 × ULN in the presence of liver metastases).
    c. Creatinine clearance ≤ 30 mL/min based on Cockroft-Gault.
    d. Serum phosphate > institutional ULN.
    e. Serum calcium outside of the institutional normal range or serum albumin-correct calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range.
    f. Potassium levels < institutional lower limit of normal; supplementation can be used to correct potassium level during the screening.
4. Has a history or presence of an abnormal ECG that in the investigator's opinion is clinically meaningful. Subjects with a screening QTcF interval > 450 milliseconds are excluded.
5. History of clinically significant or uncontrolled cardiac disease including unstable angina, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure, or arrhythmia requiring therapy. Subjects with a pacemaker and well-controlled rhythm for at least 1 month prior to first dose will be allowed.
6. History and/or current evidence of ectopic mineralisation/calcification, including but not limited to soft tissue, kidneys, intestine, myocardia, or lung, excepting calcified lymph nodes and asymptomatic arterial or cartilage/tendon calcification.
7. Current evidence of clinically significant corneal or retinal disorder confirmed by ophthalmologic examination.
8. Use of any potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is shorter) before the first dose of study drug. Topical ketoconazole was allowed.
9. Subjects with history of hypovitaminosis D requiring supraphysiologic doses to replenish the deficiency. Subjects receiving vitamin D food supplements were allowed.

Locations

This international study has enrolled participants at 67 study sites in the United States, South Korea, United Kingdom, France, Italy, Thailand, Germany, Belgium, Israel, Spain, Japan, and Taiwan. At the time of the data cutoff, enrollment was complete in all countries with the exception of Japan.

Treatments

The study FIGHT-202 was a single arm study and all participants received pemigatinib. Pemigatinib tablet was self-administered orally once daily on a 21-day cycle. Participants took pemigatinib on a 2-weeks-on/1-week-off schedule. The starting dose was 13.5 mg. Pemigatinib was to be taken after a 2-hour fast, and participants fasted for 1 additional hour after taking the study drug.

Subjects were allowed to continue administration until documented disease progression or unacceptable toxicity.

The safety follow-up following the last dose of the study drug was 30 days (+5 days).

Subjects were followed-up for overall survival following documented disease progression.

Objectives

Primary objective

The primary objective of the study FIGHT-202 is to evaluate the efficacy of pemigatinib in participants with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 rearrangements or fusions who have progressed on at least 1 previous treatment.

Secondary objectives

The secondary objectives are:

- To evaluate the efficacy of pemigatinib in participants with advanced/metastatic or surgically unresectable cholangiocarcinoma within different molecular subgroups.

- To evaluate the safety of pemigatinib in participants with advanced/metastatic or surgically unresectable cholangiocarcinoma.

- To identify and evaluate covariates that may influence the PK of pemigatinib in this participant population through population PK analysis. Additionally, exposure-response analyses for key efficacy and safety parameters may be considered if sufficient data are available.

Exploratory Objectives

Additional exploratory objectives include:

- To evaluate pharmacodynamics.

- To explore potential biomarkers.

- To evaluate the impact of pemigatinib on quality of life.

Statistical hypothesis: Since this trial is an uncontrolled phase I (II) – trial a statistical hypothesis remains missing. The primary efficacy analysis is planned to be regarding the primary endpoint of the study. This is defined as ORR in subjects with FGFR2 translocations based on the central genomics laboratory results, defined as the proportion of subjects with best response of CR or PR based on review of scans by an independent centralised radiological review committee per RECIST v1.1 (Eisenhauer et al 2009) results.

Confirmation of CR and PR is required as documented in the Independent Review Charter. This analysis will be based on efficacy evaluable population for subjects with FGFR2 translocations. Subjects who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR.

The 95% CI for ORR will be calculated using exact method for binomial distribution.

Outcomes/endpoints

Primary endpoint

The primary endpoint of this study is to determine the objective response rate (ORR) in participants with FGFR2 rearrangements or fusions based on the central genomics laboratory results (Cohort A). ORR is defined as the proportion of participants who achieved a complete response (disappearance of all target lesions) or a partial response (≥ 30% decrease in the sum of the longest diameters of target lesions) based on RECIST v1.1. Clinical response is determined by an independent review committee (IRC).

Secondary endpoints

The key secondary endpoint is DOR which corresponds to time from the date of complete response or partial response until progressive disease (in all cohorts).

The additional secondary endpoints are:

- PFS = first dose to progressive disease or death (all cohorts).
- ORR in participants with other FGF/FGFR alterations (Cohort B).
- ORR in all participants with FGF/FGFR alterations (Cohorts A and B).
- ORR in participants negative for FGF/FGFR alterations (Cohort C [United States only]).
- DCR = complete response + partial response + stable disease (all cohorts).
- OS = first dose to death due to any cause (all cohorts).
- Safety and tolerability assessed by evaluating the frequency, duration, and severity of AEs; through review of findings of physical examinations, changes in vital signs, and ECGs; and through clinical laboratory blood and urine sample evaluations (all cohorts).
- Population PK (all cohorts).

Exploratory Endpoints

Exploratory endpoints include:

- Profile tumour and blood samples for baseline and on-treatment characteristics associated with response, resistance, and safety, including examinations of plasma markers and tumour and blood cell characteristics.

- Comparison of local versus central genomic testing results.

- Quality-of-life evaluation (EORTC QLQ-C30 and EORTC QLQ-BIL21). Note: The BIL21 is only administered to participants enrolled in the US, United Kingdom, Italy, Germany, and South Korea.

Randomisation and blinding (masking)

This was a single arm, open-label study without randomisation or blinding.

Statistical methods

Analysis population

The efficacy evaluable population includes all participants who received at least 1 dose of pemigatinib and either have a known FGF/FGFR alteration or, in the United States, who are negative for FGF/FGFR alterations based on central genomics laboratory results. All efficacy analyses were conducted using the efficacy evaluable population.

The per protocol population includes participants in the efficacy evaluable population who were considered to be sufficiently compliant with the Protocol. The per protocol population was used for sensitivity analyses of ORR.

The safety population includes all enrolled participants who received at least 1 dose of pemigatinib. All safety analyses were conducted using the safety population.

Sample size

According to the original Statistical Analysis Plan, dated 12 JUN 2017, approximately 60 subjects with documentation of FGFR2 translocation from the central genomics laboratory were planned for the final analysis of the primary endpoint of ORR. With the assumed rate of 33% for the intervention, a sample size of approximately 60 subjects would provide > 80% probability to have a 95% CI with lower limit of > 15%, assuming 10% lost to follow-up. Up to 20 subjects will be enrolled in Cohort B and Cohort C (United States only), respectively, which will provide > 80% chance of observing at least 4 responders in each cohort, if the underlying ORR is 30%.

Following amendment 1 (15 APR 2019) approximately 100 participants with tumours with FGFR2 rearrangements or fusions from the central genomics laboratory were planned for analysis of the primary endpoint (ORR in participants with tumours with FGFR2 rearrangements or fusions (Cohort A) based on the central genomics laboratory results). With the assumed rate of 33% for the intervention, a sample size of approximately 100 participants provides > 95% probability to have a 95% CI with lower limit of > 15%, assuming 10% of participants are lost to follow-up; it was predetermined that the study would be considered positive if the lower limit of the 95% CI for ORR exceeded 15%.

Interim analyses and stopping rules

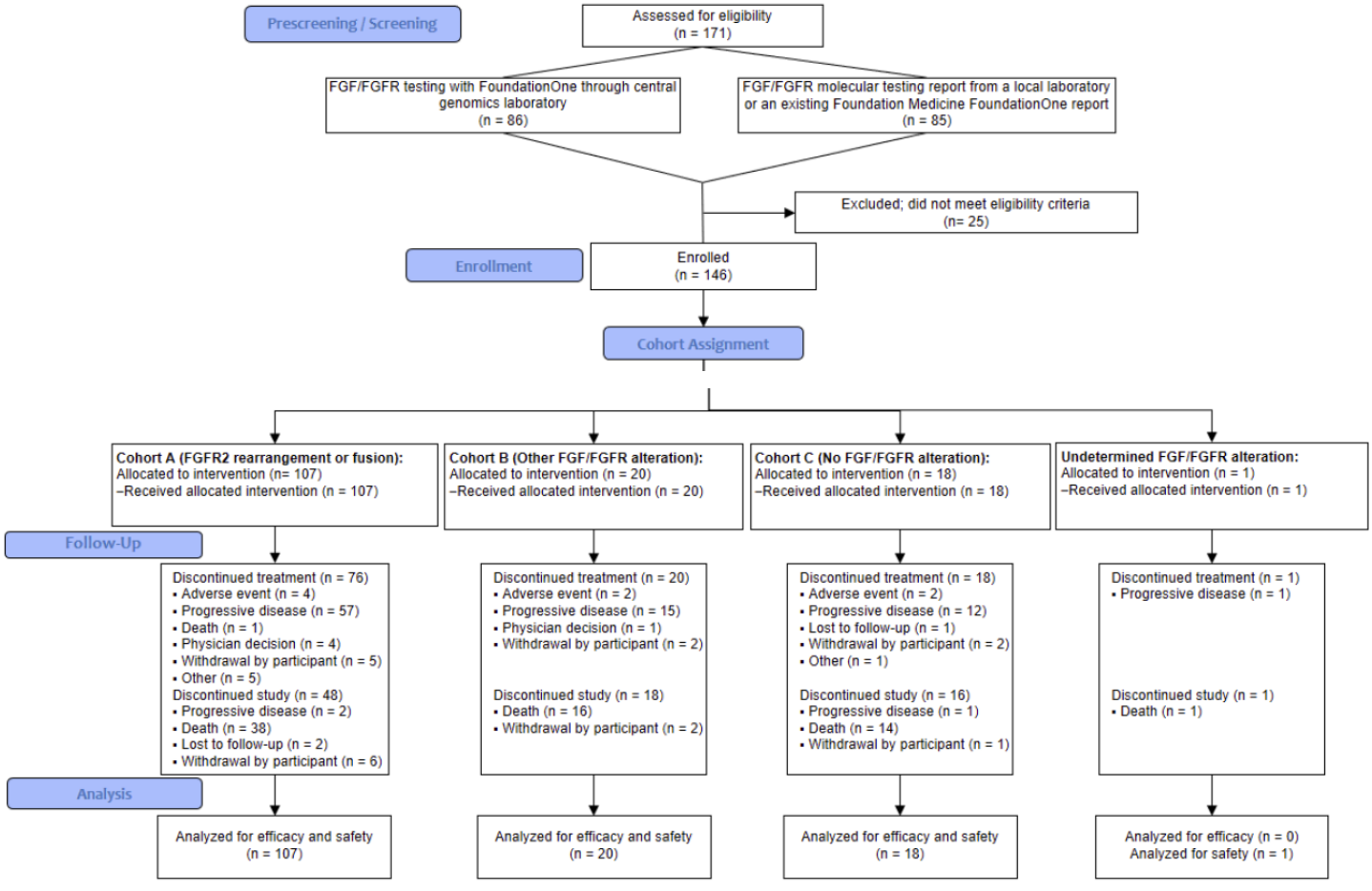
For Cohort A (FGFR2 translocation), a futility analysis was planned to be performed when approximately 25 subjects would be enrolled into the cohort and would have had at least 2 cycles of data. The rule to perform the futility analysis has been modified by amendment 1 and the futility analysis was planned to be performed when approximately 25 subjects would be enrolled into the cohort and would have had at least 1 tumour assessment or would have had permanently discontinued study treatment. Cohort A could be stopped for futility if 2 or fewer responders were observed, for which there is less than a 10% probability of claiming ORR > 15% at final analysis based on a 60-subject cohort, as initially planned before Amendment 1. This rule was just a guidance and was nonbinding.

Cohorts B (other FGF/FGFR alterations) and C (United States only; negative for FGF/FGFR alterations) could be stopped if 1 or less responders were observed within the first 10 subjects enrolled into the cohort who had at least 2 cycles of data. This rule was just a guidance and was nonbinding.

Results

Participant flow

Figure 11: Consort Diagram (Safety Population)



Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory.

Baseline data

Table 16: Summary of demographics and baseline characteristics (safety population)

Variable	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off				
	Cohort A (N = 107)	Cohort B (N = 20)	Cohort C (N = 18)	Undetermined (N = 1)	Total (N = 146)
Age (years)					
Mean (STD)	55.3 (12.02)	61.9 (10.99)	63.7 (10.68)	51.0 (N/A)	57.2 (12.08)
Median	56.0	63.0	65.0	51.0	59.0
Min, max	26, 77	45, 78	31, 78	51, 51	26, 78
Age group, n (%)					
< 65 years	82 (76.6)	10 (50.0)	7 (38.9)	1 (100.0)	100 (68.5)
65 - < 75 years	20 (18.7)	7 (35.0)	8 (44.4)	0	35 (24.0)
≥ 75 years	5 (4.7)	3 (15.0)	3 (16.7)	0	11 (7.5)
Sex, n (%)					
Male	42 (39.3)	9 (45.0)	10 (55.6)	1 (100.0)	62 (42.5)
Female	65 (60.7)	11 (55.0)	8 (44.4)	0	84 (57.5)
Region, n (%)					
North America	64 (59.8)	6 (30.0)	18 (100.0)	1 (100.0)	89 (61.0)
Western Europe	32 (29.9)	3 (15.0)	0	0	35 (24.0)
Rest of World[a]	11 (10.3)	11 (55.0)	0	0	22 (15.1)
Race, n (%)					
White	79 (73.8)	9 (45.0)	15 (83.3)	1 (100.0)	104 (71.2)
Black or African American	7 (6.5)	0	1 (5.6)	0	8 (5.5)
Asian	11 (10.3)	11 (55.0)	0	0	22 (15.1)
American-Indian/Alaska Native	0	0	1 (5.6)	0	1 (0.7)
Other[b]	4 (3.7)	0	1 (5.6)	0	5 (3.4)
Missing	6 (5.6)	0	0	0	6 (4.1)
ECOG status at baseline, n (%)					
0	45 (42.1)	7 (35.0)	7 (38.9)	0	59 (40.4)
1	57 (53.3)	10 (50.0)	8 (44.4)	1 (100.0)	76 (52.1)
2	5 (4.7)	3 (15.0)	3 (16.7)	0	11 (7.5)
Renal impairment grade at baseline[c]					
Normal	42 (39.3)	6 (30.0)	7 (38.9)	0	55 (37.7)
Mild	47 (43.9)	13 (65.0)	7 (38.9)	1 (100.0)	68 (46.6)
Moderate	18 (16.8)	1 (5.0)	3 (16.7)	0	22 (15.1)
Severe	0	0	1 (5.6)	0	1 (0.7)
Hepatic impairment grade at baseline[d]					
Normal	48 (44.9)	13 (65.0)	13 (72.2)	1 (100.0)	75 (51.4)
Mild	52 (48.6)	7 (35.0)	4 (22.2)	0	63 (43.2)
Moderate	7 (6.5)	0	1 (5.6)	0	8 (5.5)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

[a] Includes Israel, Japan, South Korea, Taiwan, and Thailand.

[b] Includes Hispanic, Latino, or Spanish (n = 1) or not reported (n = 4).

[c] Baseline renal impairment grade (normal, mild, moderate, or severe) based on eGFR (calculated using the MDRD equation): normal renal function = eGFR ≥ 90 mL/min/1.73 m^2; mild renal impairment = eGFR ≥ 60 and < 90 mL/min/1.73 m^2; moderate renal impairment = eGFR ≥ 30 to < 60 mL/min/1.73 m^2; severe renal impairment = eGFR < 30 mL/min/1.73 m^2.
[d] Degree of hepatic impairment based on National Cancer Institute Hepatic Working Group Criteria.

Table 17: Summary of baseline disease characteristics and disease history (safety population)

Variable	Cohort A (N = 107)	Cohort B (N = 20)	Cohort C (N = 18)	Undetermined (N = 1)	Total (N = 146)
Cholangiocarcinoma location, n (%)					
Intrahepatic	105 (98.1)	13 (65.0)	11 (61.1)	1 (100.0)	130 (89.0)
Extrahepatic	1 (0.9)	4 (20.0)	7 (38.9)	0	12 (8.2)
Other	0	3[a] (15.0)	0	0	3 (2.1)
Missing	1 (0.9)[b]	0	0	0	1 (0.7)
Time since diagnosis (years)					
n	107	20	18	1	146
Mean (STD)	1.57 (1.619)	1.01 (0.676)	1.52 (1.240)	1.82 (NA)	1.49 (1.481)
Median	1.28	0.73	0.98	1.82	1.10
Min, max	0.03[c], 11.1	0.2, 2.5	0.3, 4.3	1.8, 1.8	0.03, 11.1
Current TNM classification M, n (%)					
M0	16 (15.0)	0	2 (11.1)	0	18 (12.3)
M1	88 (82.2)	20 (100.0)	16 (88.9)	1 (100.0)	125 (85.6)
MX	1 (0.9)	0	0	0	1 (0.7)
Missing	2 (1.9)	0	0	0	2 (1.4)
Prior systemic therapy for cancer, n (%)					
Yes	107 (100.0)	20 (100.0)	18 (100.0)	1 (100.0)	146 (100.0)
Number of prior therapies administered in the metastatic/advanced setting, n (%)					
1	65 (60.7)	12 (60.0)	12 (66.7)	0	89 (61.0)
2	29 (27.1)	7 (35.0)	2 (11.1)	0	38 (26.0)
≥ 3	13 (12.1)	1 (5.0)	4 (22.2)	1 (100.0)	19 (13.0)
Prior radiotherapy, n (%)					
Yes	28 (26.2)	3 (15.0)	5 (27.8)	0	36 (24.7)
No	79 (73.8)	17 (85.0)	13 (72.2)	1 (100.0)	110 (75.3)
Prior surgery for cancer, n (%)					
Yes	38 (35.5)	6 (30.0)	4 (22.2)	0	48 (32.9)
No	69 (64.5)	14 (70.0)	14 (77.8)	1 (100.0)	98 (67.1)
Chronic hepatitis B history, n (%)	2 (1.9)	1 (5.0)	0	0	3 (2.1)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

[a] Includes gallbladder (n = 2) and ampulla of vater (n = 1; refer to Listing 2.4.2).
[b] At baseline, this participant had stage 4 cholangiocarcinoma (T3 N0 M1), presumed intrahepatic, with current sites of disease of liver, omentum, and peritoneum.
[c] Participant's date of diagnosis was entered incorrectly by the site. The time since diagnosis is 22.11 months, based on the correct date of diagnosis.

For cohort A, the majority of the patients (n= 73, 68.2%) presented an advanced stage disease (stage III or IV) at baseline, among them 7 patients (6.5%) presented a stage III whereas 66 patients presented a stage

IV (61.7%). While 32 patients presented a stage I or II (11 patients (10.3%) and 21 patients (19.6%), respectively).

In accordance with study eligibility criteria, all participants had advanced/metastatic or surgically unresectable disease.

Consistent with standard-of-care for cholangiocarcinoma, the most frequently reported classes of prior anticancer therapies were pyrimidine analogues (106 patients, 99.1%) and platinum compounds (101 patients, 94.4%). The most frequently administered pyrimidine analogues were gemcitabine, reported as gemcitabine (91 patients, 85.0%) or gemcitabine hydrochloride (8 patients, 7.5%) and fluorouracil (31 patients, 29.0%). The most frequently administered platinum compounds were cisplatin (81 patients, 75.7%) and oxaliplatin (41 patients, 38.3%). Twenty-eight patients (26.2%) received a prior radiotherapy and 38 patients a prior surgery (35.5%).

Relevant alterations identified by the central genomics laboratory were used for final cohort assignment for statistical analyses are summarised in the table below:

Table 18: FGF/FGFR genetic alterations identified by central genomics laboratory in ≥ 2 participants (Cohorts A and B)

FGF/FGFR Alteration, n	Cohort A (N = 107)
FGFR2-BICC1	31
FGFR2-N/A	5
FGFR2-KIAA1217	4
FGFR2-AHCYL1	3
FGFR2-ARHGAP24	2
FGFR2-AFF4	2
FGFR2-CCDC6	2
FGFR2-MACF1	2
FGFR2-NOL4	2
FGFR2-NRAP	2
FGFR2-PAWR	2
FGFR2-SLMAP	2
	Cohort B (N = 20)
FRS2 amplification	7
FGF3, FGF4, FGF19 amplification	5
FGFR2 p.C382R mutation	4

Table 19: Summary of pemigatinib exposure (safety population)

Variable	Pemigatinib 13.5 mg QD on a 2-weeks-on/1-week-off schedule				
	Cohort A (N = 107)	Cohort B (N = 20)	Cohort C (N = 18)	Undetermined (N = 1)	Total (N = 146)
Duration of exposure (days)[a]					
n	107	20	18	1	146
Mean (STD)	247.4 (170.25)	101.0 (111.91)	49.4 (38.83)	410.0	204.1 (170.66)
Median	219.0	41.5	39.0	410.0	181.0
Min, max	7, 730	7, 393	7, 142	NA	7, 730

Number of treatment cycles					
n	107	20	18	1	146
Mean (STD)	11.8 (7.93)	5.1 (4.82)	2.6 (1.85)	19.0 (N/A)	9.8 (7.91)
Median	10.0	2.5	2.0	19.0	8.5
Min, max	1, 34	1, 16	1, 7	19, 19	1, 34
Participants exposed, n (%)					
≤ 1 month	3 (2.8)	5 (25.0)	5 (27.8)	0	13 (8.9)
> 1-3 months	18 (16.8)	9 (45.0)	11 (61.1)	0	38 (26.0)
> 3-6 months	21 (19.6)	1 (5.0)	2 (11.1)	0	24 (16.4)
> 6-9 months	26 (24.3)	3 (15.0)	0	0	29 (19.9)
> 9-12 months	18 (16.8)	1 (5.0)	0	0	19 (13.0)
> 12-15 months	8 (7.5)	1 (5.0)	0	1 (100.0)	10 (6.8)
> 15-18 months	5 (4.7)	0	0	0	5 (3.4)
> 18-21 months	5 (4.7)	0	0	0	5 (3.4)
> 21-24 months	3 (2.8)	0	0	0	3 (2.1)
Patient years	72.5	5.5	2.4	1.1	81.6
Average daily dose (mg/day)[b]					
n	107	20	18	1	146
Mean (STD)	8.83 (1.444)	9.83 (1.733)	10.10 (2.694)	5.39 (N/A)	9.10 (1.765)
Median	9.00	9.73	10.53	5.39	9.14
Min, max	3.8, 13.5	6.1, 13.5	4.9, 13.5	5.4, 5.4	3.8, 13.5

Dose reductions, n (%)					
No dose reductions	83 (77.6)[c]	19 (95.0)	18 (100.0)	0	120 (82.2)
≥ 1 dose reduction	24 (22.4)	1 (5.0)	0	1 (100.0)	26 (17.8)[c]
1 dose reduction	20 (18.7)	1 (5.0)	0	0	21 (14.4)
> 1 dose reduction	4 (3.7)	0	0	1 (100.0)	5 (3.4)
Dose interruptions, n (%)					
No interruptions	58 (54.2)	12 (60.0)	14 (77.8)	0	84 (57.5)
≥ 1 interruption	49 (45.8)	8 (40.0)	4 (22.2)	1 (100.0)	62 (42.5)
1 interruption	22 (20.6)	6 (30.0)	1 (5.6)	0	29 (19.9)
> 1 interruption	27 (25.2)	2 (10.0)	3 (16.7)	1 (100.0)	33 (22.6)
Final dose (mg)[d]					
n	107	20	18	1	146
Mean (STD)	12.39 (2.054)	13.05 (1.385)	13.50 (0)	6.00 (N/A)	12.58 (1.948)
Median	13.5	13.5	13.5	6.0	13.5
Min, max	6.0, 13.5	9.0, 13.5	13.5, 13.5	6.0, 6.0	6.0, 13.5
Number (%) of participants with a final dose of 13.5 mg	82 (76.6)	18 (90.0)	18 (100.0)	0	118 (80.8)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

[a] Duration of treatment (days) = Date of last dose – Date of first dose + 1.

[b] Average daily dose (mg/day) = [Total actual dose taken (mg)] / [Duration of treatment including scheduled dose holds for intermittent schedule (days)].

[c] One participant in Cohort A and 1 participant in Cohort B had dose reductions that were not captured correctly. The correct numbers of participants with dose reductions are 25 (23.4% in Cohort A) and 28 (19.2% overall).

[d] Final dose was defined as last nonmissing dose in the study or last nonmissing dose prior to data cutoff..

Numbers analysed

The efficacy evaluable population included 145 participants who were assigned to cohorts based on tumour FGF/FGFR status from the central genomics laboratory: 107 participants with FGFR2 rearrangements or fusions (assigned to Cohort A), 20 participants with other FGF/FGFR alterations (assigned to Cohort B), and 18 participants with tumours that are negative for FGF/FGFR alterations (assigned to Cohort C). One participant was assigned to a group labeled "Undetermined" and excluded from the efficacy evaluable population because the local laboratory FGF/FGFR result could not be confirmed centrally due to technical issues with the tissue sample. The updated efficacy analysis with data cutoff of 7th April 2020 which has been provided during assessment, included 1 extra patient from the ongoing study leading to a total of 108 subjects in the efficacy evaluable population.

The per protocol population included 142 participants. Three participants in the efficacy evaluable population were excluded from the per protocol population due to protocol deviations.

The safety evaluable population included 146 patients.

Table 20: Analysis Populations (All Enrolled Participants)

Analysis population, n (%)	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off				
	Cohort A (N = 107)	Cohort B (N = 20)	Cohort C (N = 18)	Undetermined (N = 1)	Total (N = 146)
Safety population	107 (100.0)	20 (100.0)	18 (100.0)	1 (100.0)	146 (100.0)
Efficacy evaluable population	107 (100.0)	20 (100.0)	18 (100.0)	0	145 (99.3)
Per protocol population	104 (97.2)	20 (100.0)	18 (100.0)	0	142 (97.3)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

Outcomes and estimation

Primary outcome: Objective Response Rate Based on IRC Assessment (Cohort A)

In Cohort A, ORR based on IRC-assessed (data cutoff 22 March 2019), confirmed tumour responses was 35.5% (95% CI: 26.50, 45.35), including 3 complete responses (2.8%) and 35 partial responses (32.7%; see **Error! Reference source not found.**21). The study achieved the predetermined threshold for a positive outcome (lower limit of the 95% CI for ORR > 15%). The sensitivity analysis of ORR in the per protocol population was consistent with the primary analysis.

Table 21: Summary of Best Overall Response and Objective Response Rate Based on IRC Assessment According to RECIST v1.1 (Cohort A, Efficacy Evaluable and Per Protocol Populations)

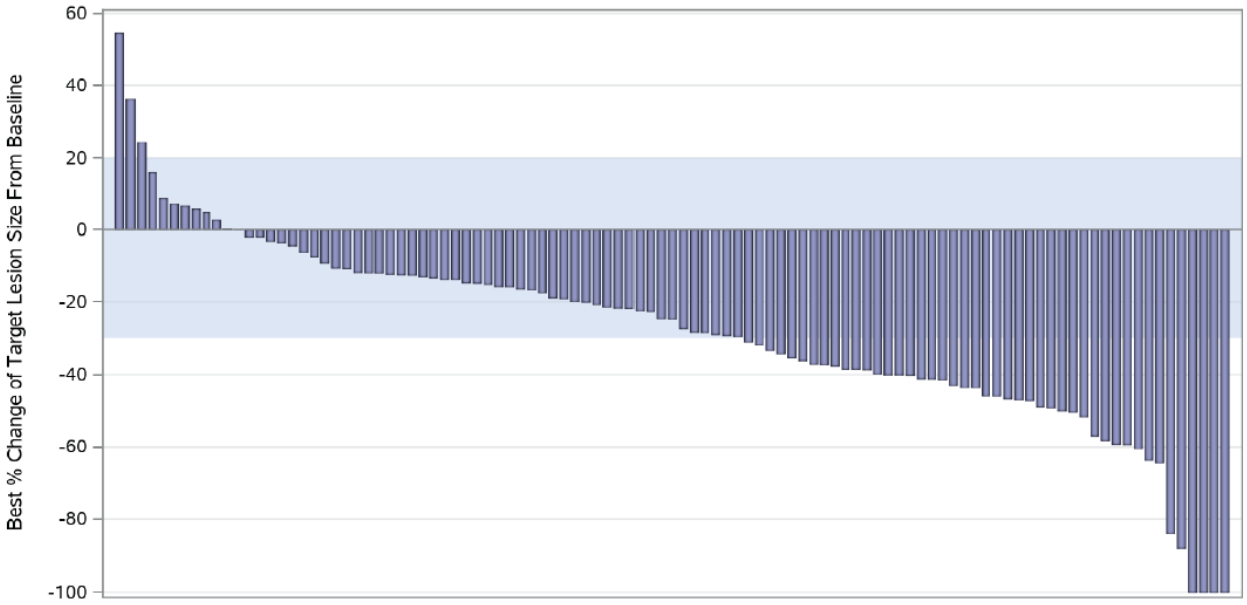
Variable	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off	
	Cohort A (FGFR2 rearrangements) Efficacy Evaluable Population (N = 107)	Cohort A (FGFR2 rearrangements) Per Protocol Population (N = 104)
Objective response[a], n (%)	38 (35.5)	37 (35.6)
95% CI[b]	26.50, 45.35	26.43, 45.57
Best overall response, n (%)		
Confirmed complete response	3 (2.8)	3 (2.9)
Confirmed partial response	35 (32.7)	34 (32.7)
Stable disease	50 (46.7)	48 (46.2)

Progressive disease	16 (15.0)	16 (15.4)
Not evaluable[c]	3 (2.8)	3 (2.9)

Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions.
[a] Participants who have best overall response of complete response or partial response.
[b] The CI was calculated based on the exact method for binomial distribution.
[c] Postbaseline tumour assessment was not performed due to study discontinuation (2 participants) or was performed prior to the minimum interval of 39 days for an assessment of stable disease (1 participant).

A majority of participants in Cohort A (91 of 103 participants with postbaseline target lesion measurements) had IRC-assessed best percentage reductions in the sum of target lesion diameters from baseline, including 45 participants with reductions of > 30% (see figure 14). Seven participants with reductions of > 30% did not have tumour assessments that met RECIST v1.1 criteria for confirmed partial response. Median best percentage change from baseline in the sum of target lesion diameters was –24.6% (range: –100% to 55%).

Figure 12: Best Percentage Change in Sum of Target Lesion Diameters From Baseline Based on IRC Assessment (Cohort A, Efficacy Evaluable Population)



Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions.
Note: Upper limit of blue shading indicates a criterion for progressive disease (≥ 20% increase in sum of target lesion diameters) and lower limit indicates a criterion for partial response (≥ 30% decrease in sum of target lesion diameters).

Updated results have been provided in response to the d180 list of outstanding issues (Data Cutoff: 07 APR 2020). The ORR in cohort A was 37.0% (95% CI: 27.94, 46.86) based on confirmed responses by an IRC. Four participants (3.7%) had complete responses and 36 participants (33.3%) had partial responses. Median DOR was 8.08 months (95% CI: 5.65, 13.14).

Table 22: Summary of Best Overall Response and Objective Response Rate in Participants With FGFR2-Rearranged Cholangiocarcinoma in Study INCB 54828-202 (07 APR 2020)

Variable	Pemigatinib 13.5 mg QD, 2-Weeks-On/1-Week-Off Schedule Cohort A, (N = 108)
Objective response[a], n (%)	40 (37.0)
95% CI[b]	27.94, 46.86
Best overall response, n (%)	
Confirmed complete response	4 (3.7)
Confirmed partial response	36 (33.3)
Stable disease	49 (45.4)
Progressive disease	16 (14.8)
Not evaluable[c]	3 (2.8)

a Participants who have best overall response of complete response or partial response according to RECIST v1.1.
b The CI was calculated based on the exact method for binomial distribution.
c Postbaseline tumour assessment was not performed due to study discontinuation (2 participants) or was performed prior to the minimum interval of 39 days for an assessment of stable disease (1 participant).

Key secondary endpoint: Duration of Response Based on IRC Assessment

Among the 38 participants in Cohort A with IRC-assessed (data cutoff 22 March 2019), confirmed tumor responses, median DOR was 7.49 months (95% CI: 5.65, 14.49).

Thirty-five of the 38 confirmed responders (92%) had at least 6 months of follow-up from the time of initial response; the other 3 confirmed responders had 5.2, 5.7, and 5.85 months of follow-up from the time of initial response as of the data cutoff.

Of the 17 participants (44.7%) who were censored for DOR, the following participants had ongoing responses at the time of last adequate tumour assessment prior to the data cutoff date:

- 3 participants had ongoing, confirmed complete responses with response durations of 4.83, 6.34, and 19.52 months
- 12 participants had ongoing, confirmed partial responses with response durations ranging from 4.17 to 14.55 months

Estimated probabilities of maintaining IRC-assessed, confirmed tumour response for at least 9 and 12 months were 47.4% (95% CI: 27.6, 64.9) and 37.4% (95% CI: 18.6, 56.2), respectively (see Table 23).

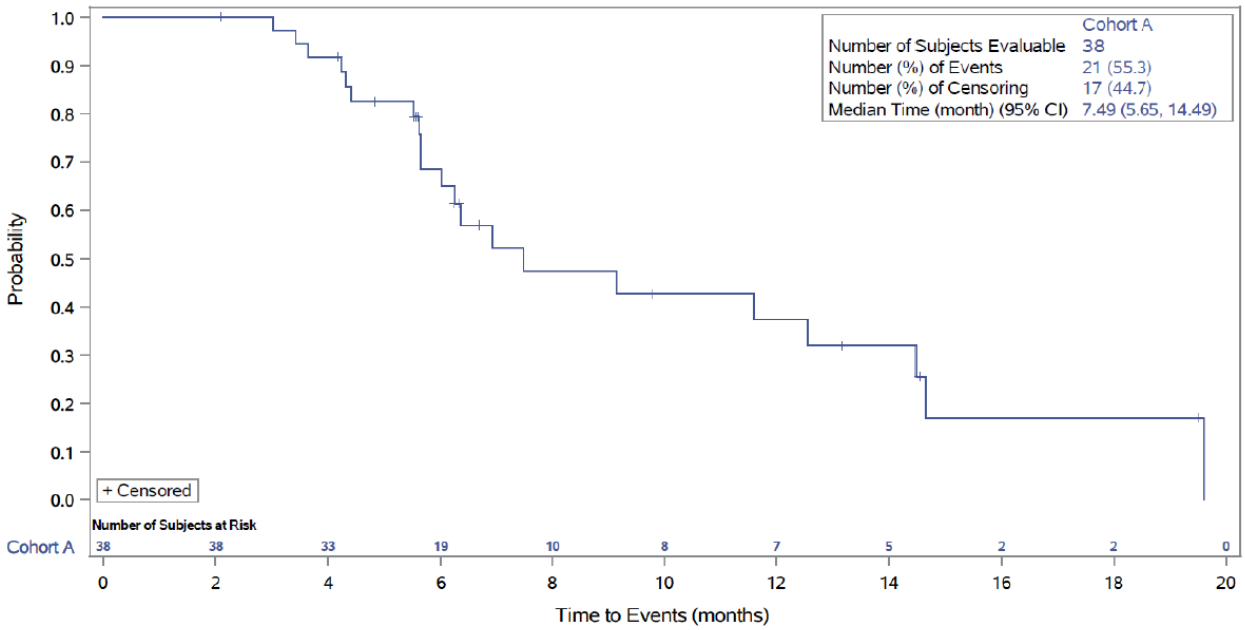
Table 23: Summary of Duration of Response Based on IRC Assessment According to RECIST v1.1 (Cohort A, Efficacy Evaluable Population)

Variable	**Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off Cohort A (FGFR2 rearrangements) [2](N = 107)**
Number (%) of participants with confirmed objective responses	38 (35.5)
Number (%) of participants with events	21 (55.3)

Disease progression	20 (52.6)
Death	1 (2.6)
Number (%) of participants censored	17 (44.7)
Median duration of response (months) (95% CI)[a]	7.49 (5.65, 14.49)
Kaplan-Meier estimates of duration of response (95% CI)	
3 months	100.0 (100.0, 100.0)
6 months	68.5 (49.0, 81.8)
9 months	47.4 (27.6, 64.9)
12 months	37.4 (18.6, 56.2)

Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions.
Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.
[a] The 95% CI was calculated using the Brookmeyer and Crowley's method (1982).

Figure 13: Kaplan-Meier Estimate of Duration of Response Based on IRC Assessment According to RECIST v1.1 (Cohort A, Efficacy Evaluable Population)



Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions.
Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.
.

As indicated above, updated results (data cutoff 7 April 2020) have been provided in response to the d180 list of outstanding issues. Observed DOR was at least 6 months in 23 responders (57.5%), at least 9 months in 15 responders (37.5%), and at least 12 months in 10 responders (25.0%).

Table 24: Summary of Duration of Response in Cohort A Based on IRC Assessment According to RECIST v1.1 (Efficacy Evaluable Population)

Variable	Cohort A (FGFR2 Rearrangements) (N = 108)
Number of participants with objective response	40
Number (%) of participants with events	27 (67.5)
Disease progression	25 (62.5)
Death	2 (5.0)
Number (%) of participants censored	13 (32.5)
Median duration of response (months) (95% CI)[a]	8.08 (5.65, 13.14)
Kaplan-Meier estimates of duration of response (95% CI)	
3 months	100.0 (100.0, 100.0)
6 months	66.0 (48.0, 79.1)
9 months	47.6 (30.2, 63.1)
12 months	37.5 (21.3, 53.7)

Note: This analysis includes responders whose initial response date was on or before 07 APR 2020. Data are from independent centralized radiological review committee per RECIST v1.1 and response is confirmed.

[a] The 95% CI was calculated using the Brookmeyer and Crowley's method (1982).

Additional secondary endpoints

a) Objective Response Rate Based on IRC Assessment in Cohorts A + B, B, and C

Table 25: Summary of Best Overall Response and Objective Response Rate Based on IRC Assessment According to RECIST v1.1 (Efficacy Evaluable Population)

Variable	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off		
	Cohort A + B (All FGF/FGFR alterations) (N = 127)	Cohort B (Other FGF/FGFR alterations) (N = 20)	Cohort C (FGF/FGFR negative) (N = 18)
Objective response[a], n (%)	38 (29.9)	0	0
95% CI[b]	22.12, 38.68	0, 16.84	0, 18.53
Best overall response, n (%)			
Confirmed complete response	3 (2.4)	0	0
Confirmed partial response	35 (27.6)	0	0
Stable disease	58 (45.7)	8 (40.0)	4 (22.2)
Progressive disease	23 (18.1)	7 (35.0)	11 (61.1)
Not evaluable[c]	8 (6.3)	5 (25.0)	3 (16.7)

Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations.

[a] Participants who have a best overall response of complete response or partial response.

[b] The CI was calculated based on the exact method for binomial distribution.

[c] Postbaseline tumour assessment was not performed due to study discontinuation (2 participants in Cohort A, 4 participants in Cohort B, 3 participants in Cohort C) or was performed prior to the minimum interval of 39 days for an assessment of stable disease (1 participant in Cohort A, 1 participant in Cohort B).

b) Progression-Free Survival Based on IRC Assessment

In Cohort A, median PFS based on IRC assessment was 6.93 months (95% CI: 6.18, 9.59).

Of the 36 participants (33.6%) who were censored for PFS, the following participants with ongoing responses or stable disease were censored at the time of last adequate tumour assessment prior to the data cutoff date):

- 3 participants with ongoing, confirmed complete responses with PFS durations of 6.24 to 22.57 months
- 12 participants with ongoing, confirmed partial responses with PFS durations of 6.87 to 19.32 months
- 13 participants with stable disease with PFS durations of 2.73 to 19.32 months

In Cohort A, Kaplan-Meier estimates of PFS at 9 and 12 months were 45.3% and 29.2%, respectively.

In Cohorts B and C, median PFS (2.10 and 1.68 months, respectively) and Kaplan-Meier estimates of PFS at evaluable timepoints were lower than in Cohort A with nonoverlapping 95% CIs.

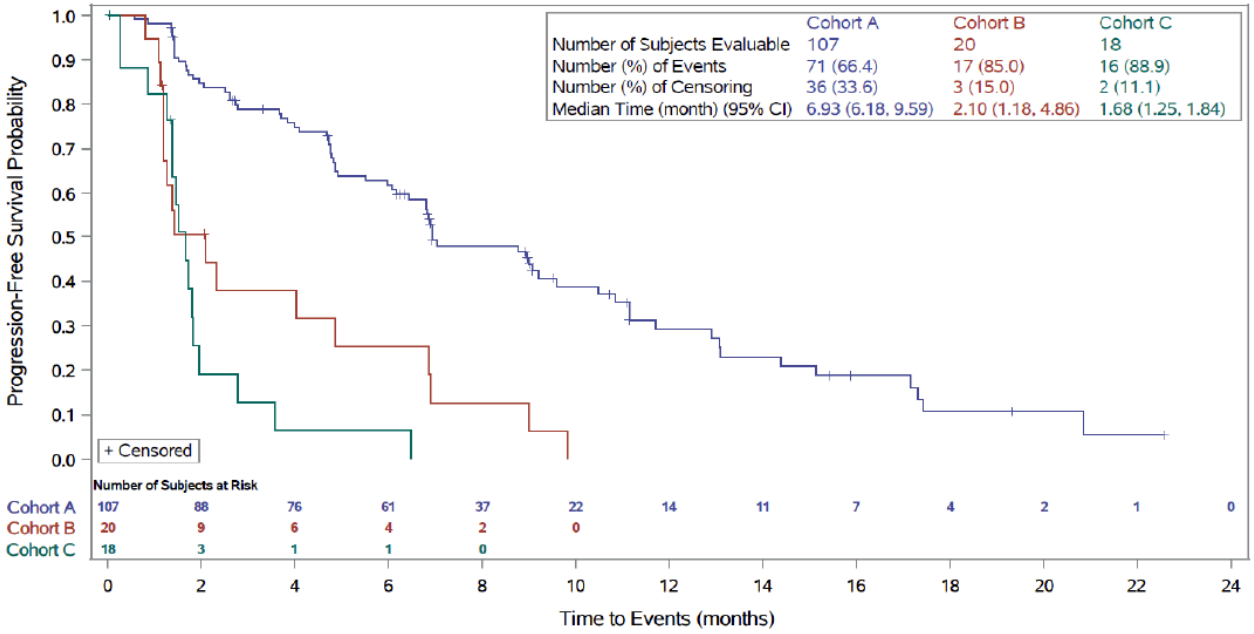
Table 26: Summary of Progression-Free Survival Based on IRC Assessment According to RECIST v1.1 (Efficacy Evaluable Population)

Variable	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off		
	Cohort A (FGFR2 rearrangements) (N = 107)	Cohort B (Other FGF/FGFR alterations) (N = 20)	Cohort C (FGF/FGFR negative) (N = 18)
Number (%) of participants with events	71 (66.4)	17 (85.0)	16 (88.9)
Disease progression	63 (58.9)	13 (65.0)	12 (66.7)
Death	8 (7.5)	4 (20.0)	4 (22.2)
Number (%) of participants censored	36 (33.6)	3 (15.0)	2 (11.1)
Median PFS (months) (95% CI)[a]	6.93 (6.18, 9.59)	2.10 (1.18, 4.86)	1.68 (1.25, 1.84)
K-M estimates (95% CI) of PFS			
3 months	78.9 (69.7, 85.5)	37.9 (16.3, 59.5)	12.7 (2.1, 33.3)
6 months	61.7 (51.5, 70.4)	25.3 (8.1, 47.1)	6.4 (0.4, 25.1)
9 months	45.3 (34.9, 55.1)	12.6 (2.1, 32.9)	0.0 (NE, NE)
12 months	29.2 (18.9, 40.2)	0.0 (NE, NE)	0.0 (NE, NE)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations. Note: Data are from IRC per RECIST v1.1.

[a] The 95% CI was calculated using the Brookmeyer and Crowley's method (1982).

Figure 14: Kaplan-Meier Estimates of Progression-Free Survival Based on IRC Assessment According to RECIST v1.1 (Efficacy Evaluable Population)



Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations. Note: Data are from IRC per RECIST v1.1.

As indicated above, updated results (data cutoff 7 April 2020) have been provided in response to the d180 list of outstanding issues. Median PFS for cohort A was 7.03 months (95% CI: 6.08, 10.48).

c) Disease Control Rate Based on IRC Assessment

In Cohort A, DCR based on IRC assessment was 82.2% (95% CI: 73.7, 89.0), including 3 participants (2.8%) with confirmed complete responses, 35 participants (32.7%) with confirmed partial responses, and 50 participants (46.7%) with stable disease maintained for a minimum of 39 days since first pemigatinib dose.

In Cohorts B and C, DCRs (40.0% and 22.2%, respectively) were lower than in Cohort A with nonoverlapping 95% CIs.

Table 27: Summary of Disease Control Rate Based on IRC Assessment According to RECIST v1.1 (Efficacy Evaluable Population)

Variable	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off		
	Cohort A (FGFR2 rearrangements) (N = 107)	Cohort B (Other FGF/FGFR alterations) (N = 20)	Cohort C (FGF/FGFR negative) (N = 18)
Disease control, n (%)[a]	88 (82.2)	8 (40.0)	4 (22.2)
95% CI[b]	73.7, 89.0	19.1, 63.9	6.4, 47.6
Best response, n (%)			
Confirmed complete response	3 (2.8)	0	0
Confirmed partial response	35 (32.7)	0	0

Stable disease ≥ 39 days	50 (46.7)	8 (40.0)	4 (22.2)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations.

[a] Participants who have a best overall response of complete response, partial response or stable disease with measurements that meet the stable disease criteria after the date of first dose at a minimum interval of 39 days.

[b] 95% CI was calculated based on the exact method for binomial distribution.

d) Overall Survival

In Cohort A, as of the data cutoff, 67 participants (62.6%) were alive and censored for OS at the last date known alive, with a median follow-up of 15.44 months (range: 7.0-24.7 months).

Median OS was 21.06 months (95% CI: 14.82, NE). Kaplan-Meier estimates of 6-month and 12-month OS were 88.6% (95% CI: 80.8, 93.4) and 67.5% (95% CI: 56.4, 76.3), respectively.

In Cohort B, as of the data cutoff (22 March 2019), 4 participants (20.0%) were alive and censored for OS at the last date known alive, with a median follow-up of 19.94 months (range: 16.2-23.5 months). Median OS was 6.70 months (95% CI: 2.10, 10.55). Kaplan-Meier estimates of 6-month and 12-month OS were lower than in Cohort A with nonoverlapping CIs (50.5% [95% CI: 26.4, 70.5] and 22.5% [95% CI: 7.0, 43.2]).

In Cohort C, as of the data cutoff (22 March 2019), 4 participants (22.2%) and censored for OS at the last date known alive, with a median follow-up of 24.18 months (range: 22.0-26.1 months). Median OS was 4.02 months (95% CI: 2.33, 6.47). Kaplan-Meier estimates of 6-month and 12-month OS were lower than in Cohort A with nonoverlapping CIs (31.3% [95% CI: 11.4, 53.6] and 12.5% [95% CI: 2.1, 32.8], respectively).

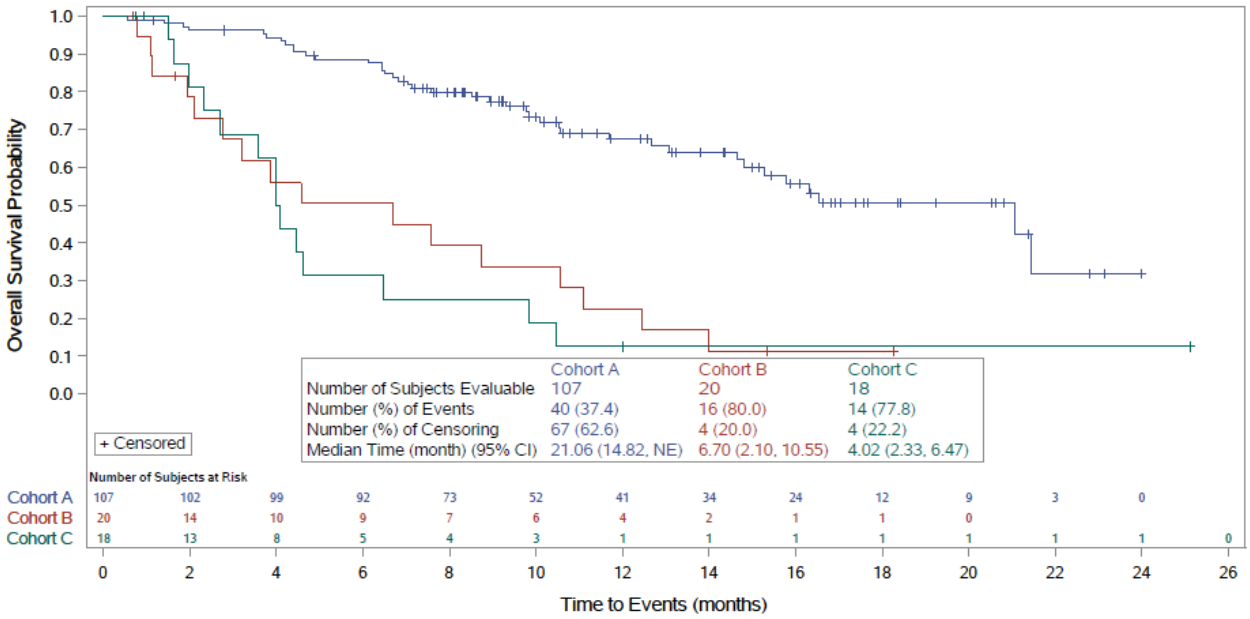
Table 28: Summary of Overall Survival (Efficacy Evaluable Population)

	INCB054828		
Variable	Cohort A (N=107)	Cohort B (N=20)	Cohort C (N=18)
Number (%) of subjects who died	40 (37.4)	16 (80.0)	14 (77.8)
Number (%) of subjects censored	67 (62.6)	4 (20.0)	4 (22.2)
Median overall survival (Months) (95% CI) [1]	21.06 (14.82, NE)	6.70 (2.10, 10.55)	4.02 (2.33, 6.47)
Kaplan-Meier estimates (95% CI) of overall survival of			
3 Months	96.2 (90.3, 98.6)	67.4 (41.2, 83.9)	68.8 (40.5, 85.6)
6 Months	88.6 (80.8, 93.4)	50.5 (26.4, 70.5)	31.3 (11.4, 53.6)
9 Months	77.4 (68.0, 84.4)	33.7 (13.9, 54.9)	25.0 (7.8, 47.2)
12 Months	67.5 (56.4, 76.3)	22.5 (7.0, 43.2)	12.5 (2.1, 32.8)

PROGRAM/OUTPUT:T_OS/T_2_2_9_OS1 DATE(TIME): 02AUG19(17:10)

Note: Cohort determination is based on FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 translocation, Cohort B = other FGF/FGFR alterations, Cohort C = negative for FGF/FGFR alterations.
[1] The 95% confidence interval is calculated using the Brookmeyer and Crowley's method (1982).
Reference: Listing 2.6.1.1

Figure 15: Kaplan-Meier Estimates of Overall Survival (Efficacy Evaluable Population)



As indicated above, updated results (data cutoff 7 April 2020) have been provided in response to the d180 list of outstanding issues. As of the data cutoff, 45 participants (41.7%) were alive and censored for OS at the last date known alive. Median OS (58.3% of the events) was an unprecedented 17.48 months (95% CI: 14.42, 22.93). Kaplan-Meier estimates of 9-month and 12-month OS were 76.1% (95% CI: 66.7, 83.2) and 67.3% (95% CI: 57.4, 75.4), respectively.

Additional endpoints

a) Time to Response and Duration of Study Treatment

Median time to response in the 38 participants in Cohort A with IRC-assessed, confirmed tumour responses was 2.69 months (range: 0.7-6.9 months). Three participants in Cohort A had target lesion reductions that did not meet the criteria for IRC-assessed, confirmed partial response until after 6 months of pemigatinib treatment.

In Cohort A, 60.7% (65/107) of participants had a duration of pemigatinib treatment > 6 months, compared with 25% of participants in Cohort B and no participants in Cohort C.

b) Endpoints Based on Investigator-Assessed, Unconfirmed Tumour Responses

Table 29: Summary of Best Overall Response and Objective Response Rate Based on Investigator Assessment According to RECIST v1.1 (Efficacy Evaluable Population)

Variable	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off		
	Cohort A (FGFR2 rearrangements) (N = 107)	Cohort B (Other FGF/FGFR alterations) (N = 20)	Cohort C (FGF/FGFR negative) (N = 18)
Objective response[a], n (%)	35 (32.7)	2 (10.0)	0
95% CI[b]	23.95, 42.45	1.23, 31.70	0, 18.53

Best response, n (%)			
Unconfirmed complete response	4 (3.7)	0	0
Unconfirmed partial response	31 (29.0)	2 (10.0)	0
Stable disease	58 (54.2)	4 (20.0)	4 (22.2)
Progressive disease	10 (9.3)	9 (45.0)	9 (50.0)
Not evaluable	2 (1.9)	0	1 (5.6)
Not assessed	2 (1.9)	5 (25.0)	4 (22.2)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations.

[a] Participants who have a best overall response of complete response or partial response.

[b] The CI was calculated based on the exact method for binomial distribution..

c) Endpoints Based on IRC-Assessed, Unconfirmed Tumour Responses

In Cohort A, ORR based on IRC-assessed, unconfirmed tumour responses was 42.1% (95% CI: 32.58, 51.99), including 4 complete responses (3.7%) and 41 partial responses (38.3%). Median DOR was 6.37 months (95% CI: 5.62, 11.60). Disease control rate was 82.2% (95% CI: 73.7, 89.0).

In Cohort B, ORR based on IRC-assessed, unconfirmed tumour responses was 10.0% (95% CI: 1.23, 31.70), with 2 participants having partial responses. Duration of response was 2.10 months in both of these participants at the time of last adequate tumour assessment. Disease control rate was 40.0% (95% CI: 19.1, 63.9). In Cohorts A and B combined, ORR based on IRC-assessed, unconfirmed tumour responses was 37.0% (95% CI: 28.61, 46.02).

In Cohort C, ORR based on IRC-assessed, unconfirmed tumour responses was 5.6% (95% CI: 0.14, 27.29), with 1 participant having a partial response with a duration of 3.71 months at the time of last adequate tumour assessment. Disease control rate was 16.7% (95% CI: 3.6, 41.4).

d) Eastern Cooperative Oncology Group Performance Status

At baseline, ECOG performance status was 0 or 1 in 92.5% of participants and 2 in 7.5% of participants. Generally, ECOG scores remained stable in the majority of participants throughout the study. Among the participants who completed the early termination visit, 4 of 61 participants (6.5%) in Cohort A, 2 of 12 participants (16.7%) in Cohort B, and 3 of 11 participants (27.3%) in Cohort C had ECOG performance status scores of 3 or 4. This indicates significant baseline ECOG differences between the arms, which mean that patients in Cohort B and C were probably significantly more affected by the disease.

e) Quality of Life

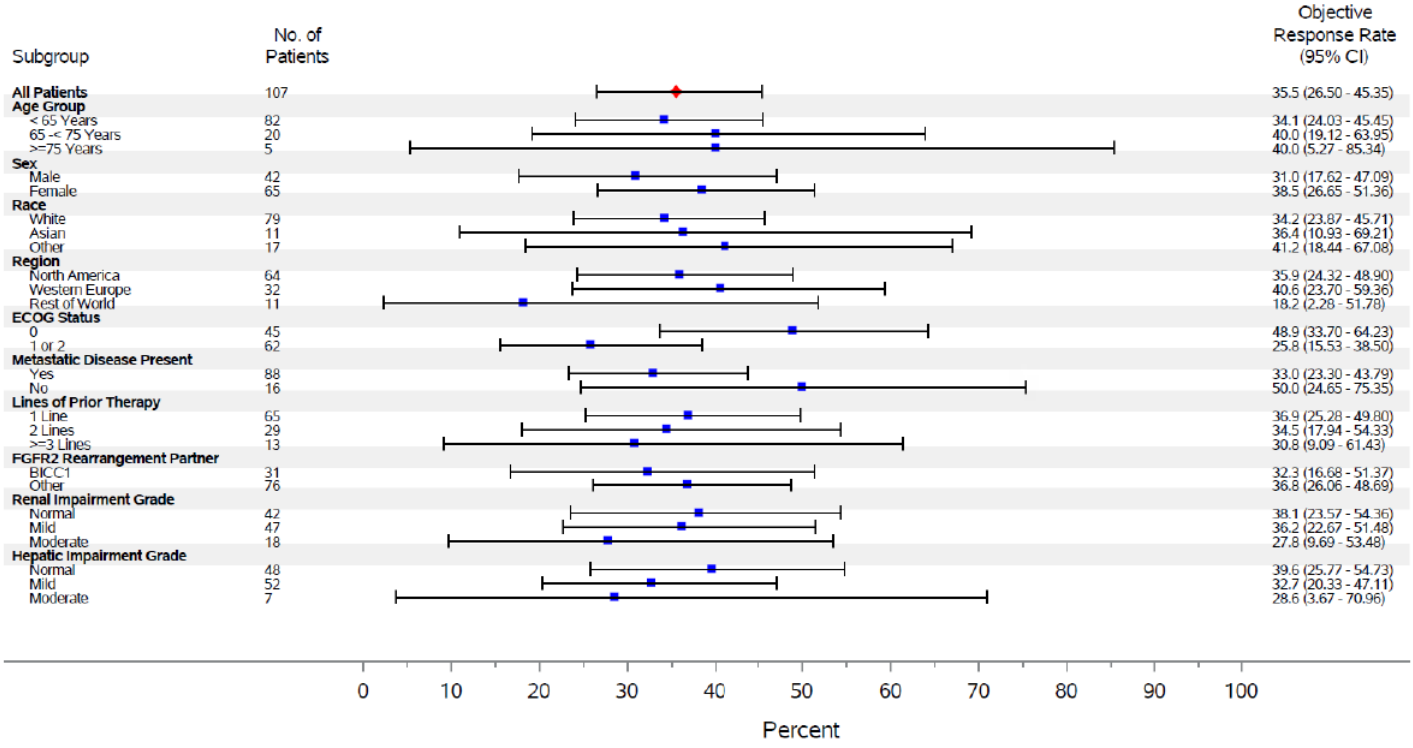
Quality of life was assessed using EORTC QLQ-C30 and QLQ-BIL21.Mean and median changes from baseline in EORTC QLQ-C30 and QLQ-BIL21 scores were variable, and no consistent trends were observed.

Ancillary analyses

a) Subgroup Analysis of Objective Response Rate

b)

Figure 16: Objective Response Rates Based on IRC Assessment According to RECIST v1.1 by Subgroup (Cohort A, Efficacy Evaluable Population)



Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions.

Note: Other races include Black or African American, Hispanic, Latino, or Spanish, not reported, or missing. Rest of World includes Israel, Japan, South Korea, Taiwan, and Thailand.

c) Subgroup Analysis of Duration of Response

Table 30: Summary of Duration of Response by Baseline Renal Impairment Grade Based on IRC Assessment According to RECIST v1.1 (Cohort A, Efficacy Evaluable Population)

	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off		
	Renal Impairment Grade		
Variable	**Normal (N = 42)**	**Mild (N = 47)**	**Moderate (N = 18)**
Number (%) of participants with confirmed objective responses	16 (38.1)	17 (36.2)	5 (27.8)
Number (%) of participants with events	9 (56.3)	10 (58.8)	2 (40.0)
Disease progression	9 (56.3)	9 (52.9)	2 (40.0)
Death	0	1 (5.9)	0
Number (%) of participants censored	7 (43.8)	7 (41.2)	3 (60.0)
Median duration of response (months) (95% CI)[a]	9.13 (5.65, 14.65)	6.93 (5.62, 14.49)	NE (3.65, NE)

Kaplan-Meier estimates of duration of response (95% CI)			
3 months	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
6 months	76.0 (42.2, 91.6)	65.5 (35.1, 84.3)	53.3 (6.8, 86.3)
9 months	56.3 (23.6, 79.5)	41.0 (15.4, 65.3)	NE (NE, NE)
12 months	45.0 (15.1, 71.4)	30.7 (8.5, 56.8)	NE (NE, NE)

Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions.

Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.

[a] The 95% CI was calculated using the Brookmeyer and Crowley's method (1982).

Table 31: Summary of Duration of Response by Baseline Hepatic Impairment Grade Based on IRC Assessment According to RECIST v1.1 (Cohort A, Efficacy Evaluable Population)

	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off		
	Hepatic Impairment Grade		
Variable	Normal (N = 48)	Mild (N = 47)	Moderate (N = 18)
Number (%) of participants with confirmed objective responses	19 (39.6)	17 (32.7)	2 (28.6)
Number (%) of participants with events	10 (52.6)	9 (52.9)	2 (100.0)
Disease progression	10 (52.6)	8 (47.1)	2 (100.0)
Death	0	1 (5.9)	0
Number (%) of participants censored	9 (47.4)	8 (47.1)	0
Median duration of response (months) (95% CI)[a]	9.13 (5.65, NE)	6.93 (3.65, 19.61)	10.99 (7.49, 14.49)
Kaplan-Meier estimates of duration of response (95% CI)			
3 months	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
6 months	71.0 (43.3, 86.9)	61.0 (28.8, 82.1)	100.0 (100.0, 100.0)
9 months	57.4 (30.2, 77.2)	33.9 (6.7, 64.8)	50.0 (0.6, 91.0)
12 months	39.3 (14.4, 63.8)	33.9 (6.7, 64.8)	50.0 (0.6, 91.0)

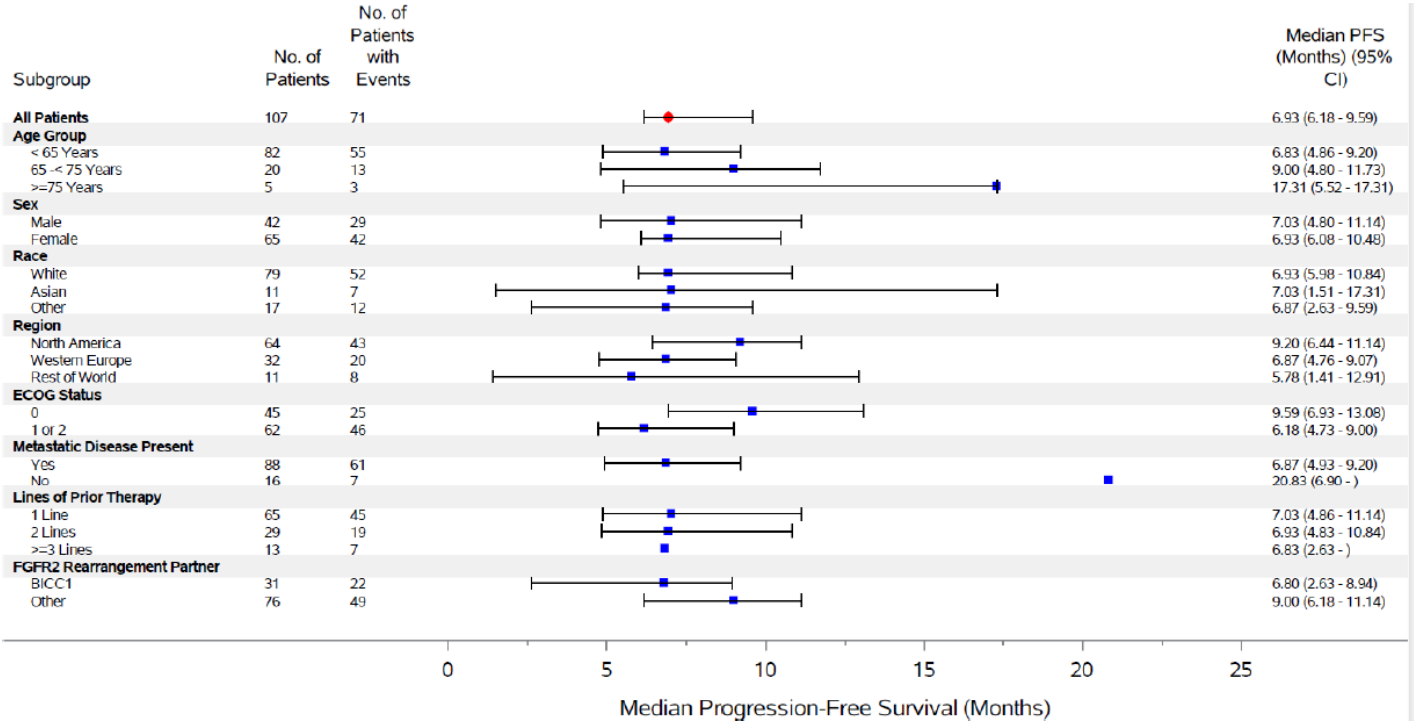
Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions.

Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.

[a] The 95% CI was calculated using the Brookmeyer and Crowley's method (1982).

d) Subgroup Analysis of Progression-Free Survival

Figure 17: Progression-Free Survival Based on IRC Assessment by Subgroup (Cohort A, Efficacy Evaluable Population)



Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory: Cohort A = FGFR2 rearrangements or fusions.
Note: Other races include Black or African American, Hispanic, Latino, or Spanish, not reported, or missing. Rest of World includes Israel, Japan, South Korea, Taiwan, and Thailand.

Summary of main efficacy results

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

Table 32: Summary of efficacy for Study INCB 54828-202 (FIGHT-202)

Title: A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy (FIGHT-202)	
Study identifier	INCB 54828-202 (FIGHT-202) NCT02924376, EudraCT Number 2016 002422-36, JapicCTI-184218
Design	Prospective, nonrandomised, open-label, multicentre clinical trial
Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	17 Jan 2017 to 22 Mar 2019 (data cutoff date) not applicable not applicable

Hypothesis	N/A (Threshold predetermined by the applicant for a positive outcome which corresponds to a lower limit of the 95% CI for ORR > 15%)		
Treatments groups	Cohort A (FGFR2 rearrangements, N= 107) Cohort B (Other FGF/FGFR alterations, N= 20) Cohort C (FGF/FGFR negative, N= 18)		Treatment: pemigatinib, 13.5 mg taken orally once daily on a 21-day cycle (on a 2-weeks-on/1-week-off schedule) Duration of treatment: until unacceptable toxicity or documented disease progression.
Endpoints and definitions	<u>Primary</u> endpoint: overall response rate (cohort A)	ORR	Proportion of participants who achieved a complete response (disappearance of all target lesions) or a partial response (⩾ 30% decrease in the sum of the longest diameters of target lesions) based on RECIST v1.1 assessed by IRC
	<u>Key secondary</u> endpoint: duration of response	DOR	Time from the date of complete response or partial response until progressive disease (in all cohorts)
	<u>Secondary</u> endpoint: progression free survival	PFS	First dose to progressive disease or death (all cohorts)
	<u>Secondary</u> endpoint: ORR in Cohort B	ORR	ORR in participants with other FGF/FGFR alterations (Cohort B)
	<u>Secondary</u> endpoint: ORR in Cohorts A and B	ORR	ORR in all participants with FGF/FGFR alterations (Cohorts A and B)
	<u>Secondary</u> endpoint: ORR in Cohort C	ORR	ORR in participants negative for FGF/FGFR alterations (Cohort C [US only])
	<u>Secondary</u> endpoint: disease control rate	DCR	Complete response + partial response + stable disease (all cohorts)
	<u>Secondary</u> endpoint: overall survival	OS	First dose to death due to any cause (all cohorts)
Database lock	22 Mar 2019/07 April 2020		

<u>Results and Analysis (data cutoff date 22 March 2019)</u>

Analysis description	**Primary Analysis**
Analysis population and time point description	Analysis population: Intent to treat

Descriptive statistics and estimate variability	Treatment group	Cohort A	Cohort B	Cohort A + B	Cohort C
	Number of	107	20	127	18
	ORR N(%) (95% CI)	38 (35.5) (26.50, 45.35)	0 (0, 16.84)	38 (29.9) (22.12, 38.68)	0 (0, 18.53)
	Median DOR months (95% CI)	7.49 (5.65, 14.49)	NA	NA	NA
	Median PFS months (95% CI)	6.93 (6.18, 9.59)	2.10 (1.18, 4.86)	NA	1.68 (1.25, 1.84)
	DCR N(%) (95% CI)	88 (82.2) (73.7, 89.0)	8 (40.0) (19.1, 63.9)	NA	4 (22.2) (6.4, 47.6)
	Median OS months (95% CI)	21.06 (14.82, NE)	6.70 (2.10, 10.55)	NA	4.02 (2.33, 6.47)
Updated Results and Analysis (data cutoff date 7 April 2020)					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Analysis population: Intent to treat				
Descriptive statistics and estimate variability	Treatment group	Cohort A			
	Number of	108			
	ORR N(%) (95% CI)	40 (37.0) (27.94, 46.86)			
	Median DOR months (95% CI)	8.08 (5.65, 13.14)			
	Median PFS months (95% CI)	7.03 (6.08, 10.48)			

	Median OS months (95% CI)	17.48 (14.42, 22.93)			
Analysis description	The primary analysis of ORR was performed in participants with tumours with FGFR2 rearrangements or fusions documented by the central genomics laboratory report (Cohort A). The 95% confidence interval (CI) for ORR was calculated using exact method for binomial distribution. It was predetermined that the study outcome would be considered positive if the lower limit of the 95% CI for ORR exceeds 15%. Secondary analyses of ORR in Cohorts A and B combined, Cohort B, and Cohort C were performed in the same way as the primary analysis of ORR. Additional secondary efficacy endpoints include DOR, PFS, DCR, and OS. Progression-free survival, DOR, and OS were analysed by the Kaplan-Meier method. Disease control rate was analysed in the same way as ORR with the exception that participants who achieved stable disease, in addition to those who achieved complete response and partial response, were included in the calculation.				
Source	Interim Study Report Trial INCB 54828-202				

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

Not applicable

Clinical studies in special populations

Table 33

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	NA	NA	NA
Non Controlled Trials	143/466	58/466	3/466

Supportive study(ies)

Not applicable

2.5.3. Discussion on clinical efficacy

The data to support this application for a conditional marketing authorisation (CMA) are based on the results of the single-arm phase 2 study INCB 54828-202 (FIGHT-202) in the second-line treatment setting and beyond of advanced/metastatic or surgically unresectable cholangiocarcinoma (CCA) with FGFR2 fusion or rearrangement.

Design and conduct of clinical studies

The study FIGHT-202 was a prospective single-arm study aimed at investigating the efficacy and safety of pemigatinib in participants with advanced/metastatic or surgically unresectable CCA who have progressed on at least 1 line of prior systemic therapy.

In general, the inclusion/exclusion criteria of the study FIGHT-202 were acceptable to reflect the target population. Participants were assigned to cohorts based on tumour FGF/FGFR status from the central genomics laboratory.

The primary endpoint of the study FIGHT-202, ORR in participants of the Cohort A with FGFR2 rearrangements or fusions based on the central genomics laboratory results, can be accepted. Nevertheless, in the context of a single-arm trial it could be difficult to disentangle the relevant clinical effect due to treatment and the possibly reported favourable prognosis of patients with FGFR2 genetic alterations.

No formal hypothesis test was pre-specified, nevertheless the power to have a 95% confidence interval for ORR with a lower limit larger than a threshold of 15% was the basis for sample size calculation and was considered as a threshold for a positive outcome according to study report. No justification was provided for this threshold.

At least two interim analyses were conducted. A pre-planned futility analysis was performed but additional, not protocol-planned interim analyses were also conducted.

Following the amendment 1 (15 APR 2019), the number of patients in cohort A was increased and the rule to perform the futility analysis has been modified. According to the scientific advice (EMA/CHMP/SAWP/546619/2019), it seems that "*the decision to increase the sample size of the cohort to be presented as pivotal evidence for the CMA from 60 to around 100 patients was taken after the cut-off of the planned efficacy analysis*". The reasons for increasing the sample size are not totally clear and the naïve calculation of the 95% CI ignoring the sample size increase leads to an incorrect coverage probability. A sensitivity meta-analysis using a fixed-effect model to estimate the 2 subgroups pooled response rate (original population of 60 patients and 47 additional patients) was provided. Conducting unplanned interim analyses and increasing sample size during an ongoing open-label study without a pre-specified plan could be acceptable.

Efficacy data and additional analyses

The efficacy evaluable population included 145 participants who were assigned to cohorts based on tumour FGF/FGFR status from the central genomics laboratory:

- Cohort A: 107 participants with FGFR2-rearranged cholangiocarcinoma
- Cohort B: 20 participants with other FGF/FGFR alterations
- Cohort C: 18 participants with tumours negative for FGF/FGFR alterations

One participant was assigned to a group labeled "Undetermined" and excluded from the efficacy evaluable population because the local laboratory FGF/FGFR result could not be confirmed centrally due to technical issues with the tissue sample. Following an amendment, enrollment and initial cohort assignment were permitted based on genomic testing results from a local laboratory. The results of the analyses comparing local versus central genomic testing have been presented and show a concordance between local and

central test for 12/14 (85.7%) subjects when a fusion was found using the local test. This result was however limited by the low number of subjects having a local laboratory report.

Efficacy in the applied target population is claimed from the outcome in Cohort A only.

Almost all the patients had an intrahepatic cholangiocarcinoma (ICC) (n=105, 98.1%), one had an extrahepatic cholangiocarcinoma (ECC) (0.9%). The frequencies of ICC and ECC among the population of the study are consistent with the literature in which the majority of FGFR2 fusion or rearrangement is observed in ICC, and which is rare in ECC (Rizvi and Gores, 2017 and Jain et al, 2018). The results observed in FIGHT-202 both in terms of response and survival are thus mainly based on the results from the sub-population of ICC. As too few patients with ECC received pemigatinib in the study FIGHT-202 and as CCA is a very heterogeneous population, it might be difficult to determine the treatment benefit in ECC sub-population. It is acknowledged from the literature that extrahepatic cholangiocarcinoma is a rare location among the cholangiocarcinoma patients with a FGFR2 fusion or rearrangement. Only one subject in Cohort A was classified as extrahepatic cholangiocarcinoma (common bile duct cancer) with an FGFR2-KIAA1217 fusion. The single patient with ECC and FGFR2 fusion had a stable disease and PFS and OS results (4.86 and 8.31 months, respectively) below the median PFS and OS in Cohort A, i.e. 6.93 months (95% CI: 6.18, 9.59) and 21.06 months (95% CI: 14.82, NE) respectively, taking into account that 46.7% of patients included in Cohort A had a stable disease too. The ongoing phase 3 study (INCB 54828-302) (Annex II condition) will provide further data on the ECC subpopulation including subgroup analysis for ECC patients with FGFR2 fusion or rearrangement further providing data for an extrapolation of efficacy and safety to this subpopulation at this time.

Baseline characteristics were generally similar between the population of the study FIGHT-202 and the population observed with FGFR genetic aberrations (GAs) by the experts in the field (Jain et al, 2018).

Quality of life data remain inconclusive because interpretation of QoL data from uncontrolled trials is mostly not informative.

Efficacy results for Cohort A

After a median follow up of 15.44 months (min, max: 7.0 to 24.7 months), out of the 107 subjects enrolled in Cohort A, a total of 3 subjects had a confirmed CR and 35 subjects had a confirmed PR (ORR 35.5%; 95% CI: 26.50, 45.35) as assessed by IRC; 50 (46.7%) had SD as a best response; disease control rate was 82.2%.

Among the 38 participants in Cohort A with IRC-assessed confirmed tumour responses, median DOR was 7.49 months (95% CI: 5.65, 14.49). All three confirmed CR are ongoing (durations of response are 4.83, 6.34, and 19.52 months), and 12 confirmed PR are ongoing (range of duration: 4.17 to 14.55 months) at the time of the data cutoff date (22 March 2019). No confirmed tumour responses were observed in participants in Cohort B (20 participants with other FGF/FGFR alterations) and in Cohort C (18 participants with tumours negative for FGF/FGFR alterations).

Formally, the study achieved the threshold predetermined by the applicant for a positive outcome (lower limit of the 95% CI for ORR > 15%).

Median time to response in the 38 participants in Cohort A with IRC-assessed, confirmed tumour responses was 2.69 months (range: 0.7-6.9 months) and 60.7% (65/107) of participants had a duration of pemigatinib treatment > 6 months.

In cohort A, the median PFS based on IRC assessment, as per Kaplan-Meier method, was estimated at 6.93 months (95% CI: 6.18, 9.59) and the median OS was 21.06 months (95% CI: 14.82, NE). Since Jain et al, 2018 have documented that FGFR alterations were associated with a longer OS compared with patients without FGFR alterations (37 v 20 months, respectively; P < .001) and this difference remained significant after excluding patients treated with FGFR inhibitors, FGFR alterations are clearly seen as a positive prognostic marker. This makes interpretation of the OS results inconclusive at the end.

In order to provide updated data on efficacy, the applicant conducted another data cut on 07 April 2020. With a median time to follow-up of 27.91 months for Cohort A patients at the time of this data cut, 10 (9.3%) patients in Cohort A were still on treatment and 98 (90.7%) had discontinued, mostly due to progressive disease (67.6%). The ORR was 37% (95% CI: 27.94, 46.86) based on confirmed responses by an IRC. Four participants (3.7%) had complete responses and 36 participants (33.3%) had partial responses. Median DOR was 8.08 months (95% CI: 5.65, 13.14). Observed DOR was at least 6 months in 23 responders (57.5%), at least 9 months in 15 responders (37.5%), and at least 12 months in 10 responders. Efficacy data are therefore confirmed and even slightly reinforced.

An analysis of the potential, not officially authorised, second line treatments used so far has been provided in order to contextualise the role of pemigatinib in the treatment of biliary tract cancers. The cisplatin plus gemcitabine combination is still considered the reference standard for patients with unresectable, metastatic, or recurrent cholangiocarcinoma. Gemcitabine has also shown activity against advanced BTCs, with response rates in the range of 12–35% when used in combination with agents such as 5-fluorouracil, cisplatin, mitomycin C, or capecitabin. A randomised phase II study also suggested that combination chemotherapy with gemcitabine and cisplatin may be more effective than gemcitabine alone (Valle et al. 2010). ORR was 24.3% for combination therapy and 15.2% for gemcitabine alone. Overall, more than 30 different second-line treatment could be found, all associated with contrasted results.
The Applicant quoted study ABC 06 (Lamarca et al. 2019), the only Phase 3, randomised, second-line study that has been found in biliary tract cancers evaluating active symptom control alone and in combination with mFOLFOX after progression on gemcitabine/cisplatin in 162 patients with locally advanced/metastatic biliary tract cancers not molecularly selected. It remains however difficult to draw conclusion from this study (ORR of 5% and DCR of 33%) since a heterogeneous population of patients with locally advanced / metastatic biliary tract cancers previously treated with cisplatin/gemcitabine chemotherapy has been enrolled. Nevertheless, this shows again the limited effect of standard chemotherapy in this advanced setting.
The meta-analysis performed by Ying et al. (2019) that included 32 trials is considered supportive to evaluate the role of second-line treatment for advanced biliary tract cancers in terms of response, overall survival and toxicities. Data show that the pooled ORR incidence of second-line therapy in pre-treated biliary tract cancers patients was 9.5% (95%CI: 7.2–12.5%). Sub-group analysis according to treatment regimens have also been performed. The pooled incidence of ORR for single targeted agent, single toxic agent (mainly fluoropyrimidine alone), fluoropyrimidine-based combination therapy, gemcitabine-based combination therapy, and taxanes-based combination therapy were 8.1%, 6.9%, 8.4%, 12.3% and 8.8% respectively. Each study is subject to limitations due to small sample size, retrospective data collection, and missing data. Nevertheless, these data provide valuable information on the characteristics and treatment outcomes of patients with and without FGFR2-driven cholangiocarcinoma.

Considering the worst-case scenario described above and taking into account the ORR of 37% (95% CI: 27.94, 46.86) observed in study FIGHT-202 Cohort A, CHMP considers that efficacy of Pemigatinib has been adequately shown.

Additional expert consultation

The scientific advisory group (SAG) consulted in the frame of pemazyre assessment provided the following view:

Currently, there are several reports indicating an association between FGFR2 alterations and better prognosis in CCA (Churi et al 2014, Graham et al 2014, Jain et al 2018, Bibeau et al 2020). However, there are no prospective data and the overall evidence is not very strong as the results are based on small retrospective series and there are also reports that did not find an association.

However, one SAG member pointed out that FGFR-2 as a prognostic favourable marker is supported by the fact that even non-responders have a remarkable OS in this trial compared to the very small cohorts B and C.

Nevertheless, the SAG agreed that an association is definitely possible. The majority of the SAG, however, considered that any favourable prognostic effect by itself would not be able to explain what for some SAG members was a very high anti-tumour activity associated with pemigatinib, based on ORR, observed CRs, tumour shrinkage in the majority of patients, intra-patient comparison of time to progression before and after pemigatinib treatment (as estimated looking at duration of prior and pemigatinib treatments).

One SAG member disagreed and considered that in the absence of a randomised trial and many biases of historical comparisons, definition of progression prior study inclusion (including intra-patient comparisons when there are no standardised rules for prior treatment discontinuation and assessment of progression), not pre-planned extension of patient numbers in Cohort A and very small number in Cohort B and C (20 and 18 pts.), the likely prognostic effect due to the patient selection based on FGFR2 fusion or rearrangement versus a drug-associated effect on important clinical outcomes, are difficult to disentangle. No relation between FGFR-2 genetic alterations (subgroups) and outcome could be demonstrated due to low numbers.

The majority of the SAG considered that the level of anti-tumour effect associated with pemigatinib, based on ORR, observed CRs, tumour shrinkage in the vast majority of patients, intra-patient comparison of time to progression before and after pemigatinib treatment (as estimated looking at duration of prior and pemigatinib treatments), in this population of patient that experienced disease progression after prior treatments, would be expected to result in a clinically relevant effect in the treated population in terms of progression-free survival, overall survival, and/or quality of life. Regrettably, though, the magnitude of such benefit cannot be estimated on the basis of a single arm trial. Further effort aiming to quantify and confirm these effects should be undertaken (see answer to question No. 5) However, at least a minimally clinically relevant effect from a patient perspective is not questioned.

One SAG member disagreed and considered that in the absence of a randomised trial and the many biases and uncertainties within the presented data (e.g. patients inclusion, definition of progression by the investigator, small patients numbers in cohort B and C with major imbalances in regions, age, intra- und extrahepatic CCA) and with historical comparisons, it cannot be concluded that there is a clear benefit in the target population, based on the available data.

There is a clear unmet medical need in the target population with commonly used regimens like the FOLFOX regimen being associated with high toxicity and low activity and efficacy. The majority of the SAG agreed that pemigatinib can address the unmet need to a clinically relevant extent from a patient perspective based on the activity observed.

One SAG member disagreed on the basis of the presented data with some uncertainties due to the absence of a randomised trial.

The SAG regretted the absence of randomised controlled trial in the target indication, to provide a better understanding of the magnitude of benefits and harms in the target population. The planned 1st line study may help address some of these uncertainties and should include a robust assessment of health-related quality of life. The SAG also regretted not being shown a comprehensive responder analysis, including Kaplan-Meier plots of OS and PFS by best overall objective response. Also, it was unclear if a comprehensive analysis of factors associated with response (including co-occurring alterations based on next-generation sequencing) has been presented. Lastly, in this single-arm trial setting without sensitive patient-level external comparisons, more careful analysis based on intra-patient comparisons should in general be recommended, beyond the visual exploration presented (a scatter plot with duration of prior v pemigatinib treatment duration could also be helpful).

The applicant company should be asked to set up a comprehensive post-marketing observational study to assess efficacy and safety objectives, to describe real-world efficacy and toxicity, and to identify factors associated with response and other outcomes, mechanisms of resistance, and risk factors for toxicity. This study should also include exploring the role of any co-occurring genomic alterations using next-generation sequencing.

Additional efficacy data needed in the context of a conditional MA

To further support the results available in the proposed indication in the scope of a CMA application, the applicant proposes confirmation of benefit-risk as a post-authorisation measure with submission of the clinical study report from an ongoing open-label randomised controlled phase 3 study Phase 3 study (INCB 54828-302). Study INCB 54828-302 will evaluate the efficacy of pemigatinib compared with the efficacy of gemcitabine plus cisplatin in a different target population, the first-line treatment of participants with FGFR2-rearranged cholangiocarcinoma and with a different frequency of administration since pemigatinib will be continuously administered compared to the 2-weeks-on/1-week-off schedule of the study FIGHT 202.

2.5.4. Conclusions on clinical efficacy

Unmet medical need could be agreed, and even if patients with FGFR2-driven disease seem to show better prognosis in the second line setting than patients without FGFR2-driven cholangiocarcinoma, the updated ORR of 37% together with the duration of response, even modest, are clearly higher than what could be observed with reference standards.

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

- In order to confirm the efficacy and safety of Pemazyre in adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that

have progressed after at least one prior line of systemic therapy, the MAH should submit the final results of study FIGHT-202 (INCB 54828-202), a phase 2 study investigating the efficacy and safety of pemigatinib in adults with advanced/metastatic or surgically unresectable cholangiocarcinoma including FGFR2 translocations who failed previous therapy. The CSR should be submitted by 31 December 2021.

- In order to confirm the efficacy and safety of Pemazyre in adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy, the MAH should submit the results of FIGHT-302 (INCB 54828-302), a phase 3 study comparing the efficacy and safety of pemigatinib vs. gemcitabine plus cisplatin chemotherapy in adults with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement. The CSR should be submitted by 31 December 2026.

2.6. Clinical safety

Introduction

The primary safety analysis for this application is based on the Phase 2, open-label, single-arm, multicentre study INCB 54828-202 in 146 patients with advanced/metastatic or surgically unresectable cholangiocarcinoma who have progressed after at least 1 previous systemic treatment (*safety population*). Together with these patients from study FIGHT-202, safety results from additional 15 cholangiocarcinoma patients from studies INCB 54828-101 and INCB 54828-102 have been pooled into the '*Cholangiocarcinoma population'* (n= 161).

Additional data in a larger homogenous phase II population is available from the phase II trial INCB 54828-201 in 184 patients (included in the All Cancer Safety Population) with a different, not applied indication (metastatic or surgically unresectable urothelial carcinoma harbouring FGF/FGFR alterations) [Efficacy results not available]. Furthermore, the database for the pooled safety analyses includes also data from participants with different types of cancer in some other small Studies INCB 54848-101, -102, -201, -202, and -203 who received pemigatinib as monotherapy and are included in the modified safety population (*All Cancer population*, N=466). Exposure and safety data from the three clinical pharmacology studies have not been pooled for the purpose of this summary of clinical safety due to differences in the study populations and the durations of exposure.

The modified safety population is composed of participants who completed at least one 21-day treatment cycle, unless the participant experienced a toxicity considered at least possibly related to pemigatinib prior to completion of the first cycle.

Safety evaluations in each of the clinical studies in participants with advanced malignancies included in this application include AE and concomitant medication monitoring, clinical laboratory tests, vital signs measurements, physical examinations, ECGs, and comprehensive eye examinations. The latter included visual acuity tests, slit-lamp examination, and funduscopy with digital imaging. Additional ophthalmologic assessments (eg, OCT) are to be performed if clinically relevant retinal findings are observed and in participants with reported visual AEs or change in visual acuity if the events or changes are suspected to be of retinal origin.

Patient exposure

A total of 562 participants have been treated with at least 1 dose of pemigatinib as monotherapy, including 484 participants with advanced malignancies.

Exposure data for pemigatinib is available from patients who received a 2-weeks-on/1-week-off therapy as an intermittent regime or from some few who had a continuous treatment schedule.

In the FIM Phase 1 trial of pemigatinib (INCB 54828-101), participants with advanced malignancies self-administer QD doses of pemigatinib; the starting dose was 1 mg administered on an intermittent schedule, which was escalated up to the maximum administered daily dose of 20 mg. Considering the doses explored in the target population, appreciable experience is only available for the 13.5 mg dose (N= 387 intermittent and N=47 for the continuous administration); mostly from the pivotal phase 2 trial INCB 54828-202. The other doses are only investigated in a small number of patients (1 to 14).

In study INCB 54828-202, the average daily dose (ADD) is mostly in line for the three cohorts but is lower than the intended daily dose of 13.5 mg (8.83, 9.83 and 10.10 mg for cohort A, B and C, respectively). It was confirmed that the ADD has been calculated including the off-treatment period of each cycle. Revised mADD (without off treatment period) was of 13.24 and 13.50 for cohort A and B & C, respectively. Overall, 76.6%, 90.0% and 100% of the patients had at a final dose of 13.5mg in cohorts A, B and C, respectively. However, 45.8%, 40.0% and 22.2% of the patients in cohorts A, B and C, respectively, had a dose reduction.

The median duration of pemigatinib exposure, including scheduled dose holds, for participants in the pivotal Study INCB 54828-202 (safety population) was 181.0 days (range: 7-730 days), and reflects 81.6 patient-years of exposure. The median durations of exposure for the Cholangiocarcinoma Population, and the All Cancer Population were 181.0, and 104.0 days respectively.

A total of 71 participants (48.6%) had > 6 months of exposure to pemigatinib, and 23 participants (15.8%) had > 12 months of exposure. At the time of the data cutoff date, 63 participants (43.2%) remained on study; 31 of these participants (21.2%) remained on pemigatinib treatment, and the remaining participants were in follow up.

Regarding patients below 18 year of age and elderly >75 years the data base has limitation.

Table 34: Summary of Pemigatinib Exposure (Safety Population)

Variable	Pemigatinib 13.5 mg QD on a 2-weeks-on/1-week-off schedule Cohort A (N = 107)	Cohort B (N = 20)	Cohort C (N = 18)	Undetermined (N = 1)	Total (N = 146)
Duration of exposure (days)[a]					
N	107	20	18	1	146
Mean (STD)	247.4 (170.25)	101.0 (111.91)	49.4 (38.83)	410.0	204.1 (170.66)
Median	219.0	41.5	39.0	410.0	181.0
Min, max	7, 730	7, 393	7, 142	NA	7, 730
Participants exposed, n (%)					
≤ 1 month	3 (2.8)	5 (25.0)	5 (27.8)	0	13 (8.9)
> 1-3 months	18 (16.8)	9 (45.0)	11 (61.1)	0	38 (26.0)
> 3-6 months	21 (19.6)	1 (5.0)	2 (11.1)	0	24 (16.4)
> 6-9 months	26 (24.3)	3 (15.0)	0	0	29 (19.9)
> 9-12 months	18 (16.8)	1 (5.0)	0	0	19 (13.0)
> 12-15 months	8 (7.5)	1 (5.0)	0	1 (100.0)	10 (6.8)
> 15-18 months	5 (4.7)	0	0	0	5 (3.4)
> 18-21 months	5 (4.7)	0	0	0	5 (3.4)
> 21-24 months	3 (2.8)	0	0	0	3 (2.1)
Patient years	72.5	5.5	2.4	1.1	81.6
Average daily dose (mg/day)[b]					
N	107	20	18	1	146
Mean (STD)	8.83 (1.444)	9.83 (1.733)	10.10 (2.694)	5.39 (N/A)	9.10 (1.765)
Median	9.00	9.73	10.53	5.39	9.14
Min, max	3.8, 13.5	6.1, 13.5	4.9, 13.5	5.4, 5.4	3.8, 13.5
Dose reductions, n (%)					
No dose reductions	83 (77.6)[c]	19 (95.0)	18 (100.0)	0	120 (82.2)
≥ 1 dose reduction	24 (22.4)	1 (5.0)	0	1 (100.0)	26 (17.8)[c]
1 dose reduction	20 (18.7)	1 (5.0)	0	0	21 (14.4)
> 1 dose reduction	4 (3.7)	0	0	1 (100.0)	5 (3.4)
Dose interruptions, n (%)					
No interruptions	58 (54.2)	12 (60.0)	14 (77.8)	0	84 (57.5)
≥ 1 interruption	49 (45.8)	8 (40.0)	4 (22.2)	1 (100.0)	62 (42.5)
1 interruption	22 (20.6)	6 (30.0)	1 (5.6)	0	29 (19.9)
> 1 interruption	27 (25.2)	2 (10.0)	3 (16.7)	1 (100.0)	33 (22.6)
Final dose (mg)[d]					
n	107	20	18	1	146
Mean (STD)	12.39 (2.054)	13.05 (1.385)	13.50 (0)	6.00 (N/A)	12.58 (1.948)
Median	13.5	13.5	13.5	6.0	13.5
Min, max	6.0, 13.5	9.0, 13.5	13.5, 13.5	6.0, 6.0	6.0, 13.5
Number (%) of participants with a final dose of 13.5 mg	82 (76.6)	18 (90.0)	18 (100.0)	0	118 (80.8)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

- Duration of treatment (days) = Date of last dose – Date of first dose + 1.
- Average daily dose (mg/day) = [Total actual dose taken (mg)] / [Duration of treatment including scheduled dose holds for intermittent schedule (days)].

- One participant in Cohort A and 1 participant in Cohort B had dose reductions that were not captured correctly. The correct numbers of participants with dose reductions are 25 (23.4% in Cohort A) and 28 (19.2% overall; see erratum).
- Final dose was defined as last non missing dose in the study or last non missing dose prior to data cut-off.

Adverse events

Table 35: Overall Summary of Treatment-Emergent Adverse Events (Safety population)

Category, n (%)	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off				
	Cohort A (N = 107)	Cohort B (N = 20)	Cohort C (N = 18)	Undetermined (N = 1)	Total (N = 146)
Participants who had a TEAE	107 (100.0)	20 (100.0)	18 (100.0)	1 (100.0)	146 (100.0)
Participants who had a treatment-related TEAE	101 (94.4)	17 (85.0)	15 (83.3)	1 (100.0)	134 (91.8)
Participants who had a serious TEAE	43 (40.2)	10 (50.0)	12 (66.7)	0	65 (44.5)
Participants who had a ≥ Grade 3 TEAE	64 (59.8)	15 (75.0)	13 (72.2)	1 (100.0)	93 (63.7)
Participants who had a fatal TEAE	3 (2.8)	2 (10.0)	1 (5.6)	0	6 (4.1)
Participants who had a TEAE leading to discontinuation of pemigatinib	5 (4.7)	3 (15.0)	5 (27.8)	0	13 (8.9)
Participants who had a TEAE leading to pemigatinib dose interruption	47 (43.9)	10 (50.0)	5 (27.8)	0	62 (42.5)
Participants who had a TEAE leading to pemigatinib dose reduction	17 (15.9)	2 (10.0)	0	1 (100.0)	20 (13.7)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

Treatment-Emergent Adverse Events

Generally, TEAEs were most frequently reported in the SOCs gastrointestinal disorders, metabolism and nutrition disorder, skin and subcutaneous tissue disorders and general disorders and administration site conditions in the total population of study FIGHT-202; most commonly reported TEAEs were hyperphosphatemia, alopecia, diarrhoea, fatigue, dysgeusia.

The most frequently reported TEAEs (>20%) in patients from cohort A were alopecia (58.9%), hyperphosphatemia (55.1%), diarrhoea (52.3%), dysgeusia (47.7%) and fatigue (44.9%), nausea (40.2%), constipation (40.2%), stomatitis (38.3%), dry mouth (38.3%), dry eye (31.8%), vomiting (30.8%), decreased appetite (29.9%), arthralgia (29.0%), dry skin (25.2%), hypophosphataemia (24.3%), pain in extremity (23.4%), back pain (22.4%) and abdominal pain (22.4%).

Overall, 63.7% (93/146) of the all patients enrolled in study FIGHT-202 reported a ⩾ Grade 3; 59.8% (64/107) of the patients in Cohort A compared to the 75.0% (15/20) and 72.2% (13/18) pf the patients in

Cohorts B and C, respectively. TEAEs ⩾ Grade 3 were most frequently reported in the SOCs gastrointestinal disorders and metabolism and nutrition disorders.

The most common reported TEAEs ≥ Grade 3 (>5%) in patients from cohort A were hypophosphataemia (12.1%), stomatitis (7.5%), arthralgia (6.5%) and palmar-plantar erythrodysaesthesia (5.6%)

Table 36: Summary of ≥ Grade 3 Treatment-Emergent Adverse Events Occurring in ≥ 2% of Participants in Study INCB 54828-202

	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off				
MedDra Preferred Term, n(%)	**Cohort A (N= 107)**	**Cohort B (N= 20)**	**Cohort C (N= 18)**	**Undetermined (N= 1)**	**Total (N=146)**
Participants who had a ≥ Grade 3	64 (59.8)	15 (75.0)	13 (72.2)	1 (100.0)	93 (63.7)
Hypophosphataemia	13 (12.1)	3 (15.0)	2 (11.1)	0	18 (12.3)
Arthralgia	7 (6.5)	2 (10.0)	0	0	9 (6.2)
Hyponatraemia	3 (2.8)	4 (20.0)	1 (5.6)	0	8 (5.5)
Stomatitis	8 (7.5)	0	0	0	8 (5.5)
Abdominal pain	5 (4.7)	0	2 (11.1)	0	7 (4.8)
Fatigue	4 (3.7)	0	3 (16.7)	0	7 (4.8)
Hypotension	4 (3.7)	2 (10.0)	0	0	6 (4.1)
Palmar-plantar erythrodysaesthesia	6 (5.6)	0	0	0	6 (4.1)
Anaemia	3 (2.8)	1 (5.0)	1 (5.6)	0	5 (3.4)
Blood alkaline phosphatase	3 (2.8)	1 (5.0)	1 (5.6)	0	5 (3.4)
Dehydration	3 (2.8)	1 (5.0)	1 (5.6)	0	5 (3.4)
Aspartate aminotransferase	3 (2.8)	0	1 (5.6)	0	4 (2.7)
Back pain	1 (0.9)	0	3 (16.7)	0	4 (2.7)
Cholangitis	3 (2.8)	0	1 (5.6)	0	4 (2.7)
Diarrhoea	3 (2.8)	0	1 (5.6)	0	4 (2.7)
Hypertension	3 (2.8)	1 (5.0)	0	0	4 (2.7)
Pleural effusion	1 (0.9)	2 (10.0)	1 (5.6)	0	4 (2.7)
Urinary tract infection	3 (2.8)	0	1 (5.6)	0	4 (2.7)
Acute kidney injury	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Alanine aminotransferase	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Ascites	2 (1.9)	1 (5.0)	0	0	3 (2.1)
Failure to thrive	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Hyperbilirubinaemia	3 (2.8)	0	0	0	3 (2.1)
Hypercalcaemia	2 (1.9)	1 (5.0)	0	0	3 (2.1)
Nausea	3 (2.8)	0	0	0	3 (2.1)
Pain in extremity	1 (0.9)	2 (10.0)	0	0	3 (2.1)
Small intestinal obstruction	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Weight decreased	2 (1.9)	1 (5.0)	0	0	3 (2.1)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

Treatment-related TEAEs occurred with similar incidences in Study INCB 54828-202 (91.8%), the Cholangiocarcinoma Population (94.4%), and the All Cancer Population (94.6%; refer to INCB 54828-202). The most common treatment-related events across the populations were similar to the most common TEAEs

overall and included hyperphosphatemia (53.4%, 57.1%, and 52.6%, respectively), alopecia (45.9%, 47.2%, and 39.9%, respectively), dysgeusia (37.7%, 38.5%, and 30.0%, respectively), diarrhea (36.3%, 34.2%, and 31.8%, respectively), fatigue (32.2%, 31.7%, and 27.7%, respectively), and stomatitis (32.2%, 32.3%, and 31.8%, respectively; refer to INCB 54828-202).

Comparison of the most frequently occurring treatment-related TEAEs for the continuous and intermittent dose regimens in the All Cancer Population suggests higher incidence (> 10% difference) of hyperphosphatemia (64.3% vs 50.5%) for continuous dosing and diarrhea (21.4% vs 33.6%) for intermittent dosing.

AESIs

In the clinical trials hyperphosphatemia, hypophosphatemia, serious retinal detachment, and nail toxicity were evaluated as clinically notable drug –related TEAEs of special interest.

To evaluate the occurrence of these events, customised aggregates of MedDRA PTs that are similar in nature were developed allowing for a more comprehensive assessment. The following PTs were identified in the integrated clinical database for the All Cancer Population:

• Hyperphosphatemia: hyperphosphatemia and blood phosphorus increased

• Hypophosphatemia: hypophosphatemia and blood phosphorus decreased

• Serous retinal detachment: chorioretinal folds, chorioretinal scar, chorioretinopathy, detachment of retinal pigment epithelium, macular oedema, maculopathy, retinal detachment, retinal disorder, retinal oedema, retinal exudates, retinal pigmentation, retinal thickening, retinopathy, serous retinal detachment, and subretinal fluid

• Nail toxicity: fungal paronychia, nail bed bleeding, nail bed tenderness, nail discoloration, nail discomfort, nail disorder, nail dystrophy, nail hypertrophy, nail infection, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia.

Nail Toxicity

The majority of nail toxicity events were Grade 1 or 2 in severity. None of the event were serious or led to discontinuation. The number of dose interruptions and dose reduction in the total population due to these AEs is relatively low (4.1% and 3.4%, respectively).

The most reported events (⩾ 5%) in cohort A were onychomadesis (12.1%), nail discolouration (11.2%), onycholisis (9.3%), nails dystrophy (9.3%), paronychia (8.4%) and onychoclasis (8.4%).

Table 37. Summary of Clinically Notable Treatment-Emergent Adverse Events of Nail Toxicity (Safety Population)

	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off					
Category MedDRA Preferred Term, n (%)	**Cohort A (N = 107)**	**Cohort B (N = 20)**	**Cohort C (N = 18)**	**Undetermined (N = 1)**	**Total (N = 146)**	
	All Grade	**All Grade**	**All Grade**	**All Grade**	**All Grade**	**≥ Grade 3**
Nail toxicity	56 (52.3)	4 (20.0)	2 (11.1)	0	62 (42.5)	3 (2.1)
Nail discolouration	12 (11.2)	1 (5.0)	1 (5.6)	0	14 (9.6)	1 (0.7)

Onychomadesis	13 (12.1)	1 (5.0)	0	0	14 (9.6)	0
Onycholysis	10 (9.3)	2 (10.0)	1 (5.6)	0	13 (8.9)	0
Nail dystrophy	10 (9.3)	1 (5.0)	0	0	11 (7.5)	0
Paronychia	9 (8.4)	1 (5.0)	0	0	10 (6.8)	1 (0.7)
Onychoclasis	9 (8.4)	0	0	0	9 (6.2)	1 (0.7)
Nail disorder	5 (4.7)	0	0	0	5 (3.4)	1 (0.7)
Onychomycosis	4 (3.7)	0	0	0	4 (2.7)	0
Nail ridging	3 (2.8)	0	0	0	3 (2.1)	0
Nail toxicity	3 (2.8)	0	0	0	3 (2.1)	0
Nail hypertrophy	1 (0.9)	0	0	0	1 (0.7)	0
Nail infection	1 (0.9)	0	0	0	1 (0.7)	0
Onychalgia	1 (0.9)	0	0	0	1 (0.7)	0

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

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Nail toxicity events leading to pemigatinib dose interruption occurred in 4.1%, 5.0%, and 4.7% of participants in Study INCB 54828-202, the Cholangiocarcinoma Population, and the All Cancer Population, respectively, and events leading to dose reduction occurred in 3.4%, 3.7%, and 3.2%, respectively.

Hyperphosphatemia

Hyperphosphatemia events were reported in 60.3% of the total population in Study INCB 54828-202; 57.9% in cohort A compared to 65.0% and 66.7% in cohort B and C, respectively. None of these events were ≥ grade 3 in severity, serious, or led to discontinuation. Reported frequency of dose interruption (1.4%) and dose reduction were low, 1.4% and 0.2%, respectively.

Hyperphosphatemia events were the most frequently occurring TEAEs in Study INCB 54828-202 (60.3%), the Cholangiocarcinoma Population (62.7%), and the All Cancer Population (59.4%) and occurred in a higher proportion of participants treated with pemigatinib on a continuous schedule than on an intermittent schedule (68.6% vs 57.8% of participants in the All Cancer Population).

The majority of these events were Grade 1 or 2 in severity and nonserious. Hyperphosphatemia events of ≥ Grade 3 severity occurred in 4 participants in the All Cancer Population, and serious events of hyperphosphatemia occurred in 2 participants in the All Cancer Population. All but one of these events, which occurred in 5 unique participants, had resolved as of the data cutoff date.

No participant discontinued pemigatinib due to a hyperphosphatemia event, and events leading to dose interruption occurred only in a low number of subjects (1.4%, 3.1%, and 3.6% of participants in Study INCB 54828-202, the Cholangiocarcinoma Population, and the All Cancer Population, respectively). Also dose reduction (0%, 0.6%, and 0.9%, respectively) were infrequent.

High phosphate levels can cause, via effects on calcium, extraskeletal deposition of calcium- phosphate crystals and electrical hyperexcitability (Peppers et al 1991). However, the clinical consequences of patients that reported hyperphosphatemia events has not been addressed

Among the 5 participants with serious and/or ≥ Grade 3 TEAEs of hyperphosphatemia, potential clinical sequelae included muscle spasms (Grade 1) and corneal opacity (Grade 1), both considered related to pemigatinib, in a participant with ongoing AEs of punctate keratitis, vitreous detachment, and intraocular lens implant with onset 6 days before the first dose of pemigatinib and 2 Grade 2 events of ECG QT prolonged in another participant (both rather not related).

No other potential sequelae were identified among participants with serious and/or ≥ Grade 3 TEAEs of hyperphosphatemia, and medical review of all cases of seizure and the other cases of ECG QT prolonged in participants in the All Cancer Population did not suggest a relationship to pemigatinib. In addition, TEAEs of calciphylaxis (with concurrent peripheral venous disease) and calcinosis cutis occurred in a single participant each.

The effectiveness of management actions and preventive measures could have been called into question as hypophosphatemia events were also reported at a high frequency and hypophosphatemia was the most common ≥ Grade 3 TEAE reported in the cholangiocarcinoma Population (see below).

Hypophosphatemia

In Study INCB 54828-202, hypophosphatemia events were reported in 25.2% of the total population; 25.2% in cohort A compared to 20.0% and 11.1% in cohort B and C, respectively. These events were ⩾ grade 3 in 12.3% of the total population. None of the events of hypophosphatemia were serious, led to discontinuation, or led to dose reduction. Dose interruption was reported in 1.4% of participants. TEAEs of hypophosphatemia ⩾ Grade 3 by cohorts were not provided.

The incidence of TEAEs of hypophosphatemia was similar for participants in Study INCB 54828-202 (22.6%) and in the Cholangiocarcinoma Population (26.7%) and was lower for the All Cancer Population (14.4%). Comparison of the intermittent and continuous dose regimens showed a higher incidence of hypophosphatemia in the intermittent schedule (15.7% vs 7.1%).

Hypophosphatemia was the most common ≥ Grade 3 TEAE among participants in Study INCB 54828-202 (12.3%) and the Cholangiocarcinoma Population (14.3%) and the second most common ≥ Grade 3 TEAE among participants in the All Cancer Population. A total of 3 participants interrupted pemigatinib due to a TEAE of hypophosphatemia. Two of the 3 events had resolved as of the data cutoff date, and 1 remained ongoing.

Serous Retinal Detachment

In Study INCB 54828-202, serous retinal detachment was reported in 4.1% of the total population; 3.7% (4/107) in cohort A compared to 5.0% (1/20) and 5.6% (1/18) in cohort B and C. Only one case in cohort A was serious but was resolved with sequelae in few days after interruption of pemigatinib and necessary medical corrective actions.

Serous retinal detachment events, most commonly reported as serous retinal detachment or detachment of retinal pigment epithelium, occurred in 5.6% of participants in the Cholangiocarcinoma Population, and 7.5% of participants in the All Cancer Population. Overall, ≥ Grade 3 events included detachment of retinal pigment epithelium in 1 participant and retinal detachment in 2 participants. The majority of the events were Grade 1-2 in severity. However, the minimal severity grade to categorise events reported as 'Retinal detachment' is grade 3 according CTEAE v5.0.

Serous retinal detachment events led to discontinuation of pemigatinib in 2 participants (0.4% of the All Cancer Population), including the participant with the serious TEAE of detachment of retinal pigment epithelium above and a participant in Study INCB 54828-201 with Grade 1 events of subretinal fluid and retinal disorder that were ongoing at the time of the data cutoff date.

Serous retinal detachment events leading to pemigatinib dose interruption occurred in 0.7%, 0.6%, and 1.7% of participants in Study INCB 54828-202, the Cholangiocarcinoma Population, and the All Cancer Population, respectively, and events leading to dose reduction occurred in 0.4% of participants in the All Cancer Population and no participants in Study INCB 54828-202 or the Cholangiocarcinoma Population.

Additional Eye Disorders

The most common TEAEs reported under the SOC eye disorders was dry eyed, reported in 25.3% of the total population in Study INCB 54828-202, and in 31.8% of the patients in cohort A. In cohort B and C the reported frequency was lower, 5.0% and 5.6%, respectively. Other events under eye disorders of relevance that were reported in ≤5% in patients of cohort A are blepharitis (4.7%), eye pain (4.7%), vitreous floaters (3.7%), cataract (3.7%), vision blurred (3.7%), vision blurred (3.7%), keratitis (2.8%), visual impairment (2.8%), vitreous detachment (2.8%).

Serious adverse event/deaths/other significant events

Serious TEAES were reported in 44.5% (65/146) of all the enrolled patients of study FIGHT-202; 40.2% in cohort A compared to 50.0% and 66.7% in cohorts B and C, respectively. The most frequently reported events (>10%) in the total enrolled population pertaining to SOCs Gastrointestinal disorders and Infections and infestations. The most frequently reported serious evens (>2%) in cohort A were pyrexia (4.7%), abdominal pain (3.7%), cholangitis (3.7%) and cholangitis infective (2.8%).

Serious TEAEs (including serious events with a fatal outcome) occurred in similar proportions of participants in Study INCB 54828-202 (**44.5%**) and in the Cholangiocarcinoma and All Cancer Populations (41.6% for both pooled populations). The most frequently reported events pertaining to SOCs Gastrointestinal disorders and Infections and infestations.

In study INCB 54828-202, 6 cases (4.1%) of serious TEAEs from the all patients enrolled led to fatal outcomes; 3 cases in cohort A, 2 cases in cohort B and 1 case in cohort C. These events were classified in SOCs hepatobiliary disorders, infections and infestations, metabolism and nutrition disorders and respiratory, thoracic and mediastinal disorders. The three fatal cases in cohort A were due to bile duct obstruction and failure to thrive. Serious TEAEs with a fatal outcome occurred with similar incidences in Study INCB 54828-202 (4.1%) and the Cholangiocarcinoma Population (4.3%). Across all 3 safety populations, **only 1 death was considered related to pemigatinib by the investigator**. This was a cerebrovascular accident in a participant in the All Cancer Population. However, causality assessment for the event was confounded by a concurrent cardiovascular condition (patent foramen ovale), obesity, and hypothyroidism.

Laboratory findings

Clinical Haematology

In study INCB 54828-202, treatment-emergent worsening of haematology parameters most reported (≥ 10%) in cohort A were decreased haemoglobin (42.1%), lymphocytes (32.7%), platelets (32.7%), leukocytes (26.2%) and neutrophils (10.3%). Contrary, leukocytes increase were reported in 26.2% of the patients in the same cohort. Reported frequencies of these events are mostly in line for cohort B and C.

Mostly maximum worsening from baseline of these events were grade 3; reported incidence of these events shifting to grade 4 is relatively low.

Decreased leukocytes were reported in 22.4% whereas increased leukocytes were also reported in 26.2% of the patients in cohort A. One patient with increased leukocytes was Grade 3 (0.9%); the rest were not graded. Two patients with decreased leukocytes were grade 3 or 4 (1.8%). There were no adverse events reported in any of these patients that could be related to the aberrant leukocyte results. Subjects with cholangiocarcinoma can develop various infections in and around their stents or in the bile ducts. Fluctuation of the leukocytes may account for infections related to the disease state.

Table 38. Treatment-Emergent Worsening of CTC-Graded Haematology Parameters (Safety Population)

Laboratory parameter, n (%)	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off						
	Cohort A (N= 107)	Cohort B (N= 20)	Cohort C (N= 18)	Undetermined (N= 1)	Total (N=146)		
	All Grade	All Grade	All Grade	All	All Grade	Grade 3	Grade 4
Haemoglobin (decreased)	45 (42.1)	8 (40.0)	9 (50.0)	1 (100.0)	63 (43.2)	8 (5.5)	NA
Lymphocytes (decreased)	35 (32.7)	10 (50.0)	6 (33.3)	0	51 (34.9)	11 (7.5)	1 (0.7)
Platelets (decreased)	35 (32.7)	4 (20.0)	2 (11.1)	0	41 (28.1)	2 (1.4)	3 (2.1)
Leukocytes (increased)	28 (26.2)	7 (35.0)	5 (27.8)	0	40 (27.4)	1 (0.7)	NA
Leukocytes (decreased)	24 (22.4)	1 (5.0)	1 (5.6)	0	26 (17.8)	1 (0.7)	1 (0.7)
Lymphocytes (increased)	10 (9.3)	1 (5.0)	1 (5.6)	0	12 (8.2)	3 (2.1)	NA
Neutrophils (decreased)	11 (10.3)	1 (5.0)	0	0	12 (8.2)	0	1 (0.7)
Haemoglobin (increased)	1 (0.9)	0	0	0	1 (0.7)	1 (0.7)	NA

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

Note: Worst CTC grade postbaseline. If baseline grade is missing, any postbaseline abnormality (Grade 1-4) is considered worsening from baseline. NA indicates Grade 4 CTC grade is not applicable to the parameter.

Clinical Chemistry

In study INCB 54828-202, treatment-emergent worsening of chemistry parameters most reported (≥ 30%) in cohort A were creatinine increased (99.1%), phosphate decreased (74.8%), ALT increased (44.9%), AST increased (43.0%), calcium increased (46.7%), ALK increased (40.2%), glucose increased (38.3%), sodium decreased (32.7%), urate increased (32.7%) and albumin decreased (30.8%)

Alterations in phosphate were mostly decreases of baseline levels during the course of treatment.

Table 39: Treatment-Emergent Worsening in CTC-Graded Chemistry Parameters

	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off						
	Cohort A (N= 107)	Cohort B (N= 20)	Cohort C (N= 18)	Undetermined (N= 1)	Total (N=146)		
Category, n (%)	All Grades	All Grades	All Grades	All Grades	All Grades	Grade 3	Grade 4
Creatinine increased[a]	106 (99.1)	19 (95.0)	17 (94.4)	1 (100.0)	143 (97.9)	2 (1.4)	0
Phosphate decreased	80 (74.8)	13 (65.0)	5 (27.8)	1 (100.0)	99 (67.8)	54 (37.0)	1 (0.7)
Alanine aminotransferase increased	48 (44.9)	12 (60.0)	3 (16.7)	0	63 (43.2)	6 (4.1)	0
Aspartate aminotransferase increased	46 (43.0)	7 (35.0)	8 (44.4)	1 (100.0)	62 (42.5)	9 (6.2)	0
Calcium increased	50 (46.7)	8 (40.0)	4 (22.2)	0	62 (42.5)	5 (3.4)	1 (0.7)
Alkaline phosphatase increased	43 (40.2)	10 (50.0)	7 (38.9)	0	60 (41.1)	16 (11.0)	0
Sodium decreased	35 (32.7)	13 (65.0)	8 (44.4)	1 (100.0)	57 (39.0)	14 (9.6)	3 (2.1)
Glucose increased	41 (38.3)	8 (40.0)	3 (16.7)	1 (100.0)	53 (36.3)	1 (0.7)	0
Albumin decreased	33 (30.8)	10 (50.0)	6 (33.3)	0	49 (33.6)	0	NA
Urate increased	35 (32.7)	6 (30.0)	3 (16.7)	0	44 (30.1)	NA	14 (9.6)
Bilirubin increased	31 (29.0)	4 (20.0)	2 (11.1)	1 (100.0)	38 (26.0)	7 (4.8)	1 (0.7)
Potassium decreased	28 (26.2)	5 (25.0)	4 (22.2)	1 (100.0)	38 (26.0)	5 (3.4)	2 (1.4)
Calcium decreased	15 (14.0)	7 (35.0)	3 (16.7)	0	25 (17.1)	0	4 (2.7)
Potassium increased	14 (13.1)	3 (15.0)	1 (5.6)	0	18 (12.3)	1 (0.7)	2 (1.4)
Glucose decreased	15 (14.0)	0	0	1 (100.0)	16 (11.0)	0	2 (1.4)
Sodium increased	8 (7.5)	1 (5.0)	1 (5.6)	0	10 (6.8)	0	0
Triglycerides increased	4 (3.7)	0	1 (5.6)	0	5 (3.4)	0	0

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.
Note: Worst CTC grade postbaseline is summarised; if baseline grade is missing, any postbaseline abnormality (Grade 1-4) is considered worsening from baseline. NA indicates Grade 4 CTC is not applicable to the parameter.
[a] CTC grade based on changes relative to the ULN and baseline values.

Abnormal laboratory values for calcium, vitamin D, sodium and PTH were reported and clinical consequences of these metabolic dysregulation both at short and long-term are currently unknown.

Vital Signs, Physical Examinations, and Other Observations Related to Safety

Most participants had normal vital signs measurements at baseline and at all timepoints assessed.

The most frequently occurring abnormal vital signs values for participants in Study INCB 54828-202 and participants in the All Cancer Population were increases in pulse. The primary evaluation of potential effects of pemigatinib on cardiac function is based on timed 12-lead ECGs, which were performed during PK

sampling in 116 participants from Study INCB 54828-101. According to the data available, pemigatinib has no relevant effect on cardiac conduction (ie, PR and QRS intervals) and analysis of clinical events (Torsade de pointes/QT prolongation SMQ/VT and seizures) seems confirmative.

Criteria for alert-vital-signs were measured values that were outside the normal range with > 25% change from baseline. Alert values were reported most frequently for pulse measurements (18 participants). In addition, 6 participants had on-study (excluding follow-up) systolic blood pressure measurements that met alert criteria, and 2 participants had an on-study diastolic blood pressure measurements that met alert criteria. No participants had body temperatures or respiratory rates that met alert criteria. Premature atrial conduction and premature ventricular contractions were observed in monkey during safety pharmacology studies.

In cases where CT/MRI findings were available, the most common findings were calcium deposits in the subcutaneous tissue in the abdomen, buttocks or lower extremities, and/or the vascular compartment. There were no reported findings of visceral soft-tissue mineralisation of the heart, lung, liver, adrenal glands, or any other organ.

Safety in special populations

A comparison of the overall incidences of ≥ Grade 3 TEAEs, serious TEAEs, and TEAE leading to dose interruptions or reductions for participants < 65 years of age and participants 65 to < 75 years of age shows that larger proportions of the older participants had at least 1 event in each of these age categories.

Male participants had a higher incidence of serious TEAEs than female participants. But the most frequently occurring TEAEs were similar for the 2 sex groups but occurred in larger proportions of women: hyperphosphatemia (67.7% vs 50.8%), alopecia (60.4% vs 35.4%), diarrhea (51.0% vs 36.9%), nausea (44.8% vs 27.7%), and vomiting (28.1% vs 18.5%). For ⩾ Grade 3 TEAEs, the most frequently occurring events, including hypophosphatemia, hyponatremia, arthralgia, and palmar-plantar erythrodysesthesia syndrome, were similar for the 2 sex subgroups.

Since 72.0% of participants were White outcome regarding race is not interpretable.

Similarly, the quality of data precludes any reasoned conclusion regarding drug related TEAE differences in the few patients with renal and hepatic impairment. The incidences of TEAEs of blood creatinine increased, diarrhea, and dysgeusia, increased with worsening renal impairment, while the incidences of hyperphosphatemia and hypophosphatemia decreased with worsening renal impairment. The overall TEAE profile of pemigatinib was similar for participants with normal hepatic function and mild hepatic impairment, while patients with severe hepatic impairment were excluded.

For baseline ECOG performance status subgroups the differences that were observed tended to be differences that would be expected in participants in poorer health.

There was no difference across the regions for the Cholangiocarcinoma Population in the overall incidence of TEAEs, and the most frequently occurring TEAEs were generally similar for each region although the incidences of some common events were sometimes variable, as can be expected due to the size differences in the subgroups.

Safety of pemigatinib in participants less than 18 years of age has not been evaluated, since cholangiocarcinoma is extremely rare in the paediatric population.

Table 40: Safety in special populations

Population	Demographic Characteristic	Subgroup	N	Treatment-Emergent Adverse Events, n (%)						
				All	≥ Grad	Serious	With a Fatal Outco	Leading to Study Drug	Leading to Study Drug	Leading to Study Drug Discontinuati
Cholangiocarcinoma Population (N = 161)	Age	< 65 years	110	110	63	40	4 (3.6)	39 (35.5)	14	11 (10.0)
		65 to < 75	4	40	31	22	3 (7.5)	25 (62.5)	9	1 (2.5)
		≥ 75 years	1	11	6	5	0	4 (36.4)	0	1 (9.1)
	Sex	Men	6	65	40	31	3 (4.6)	29 (44.6)	8	8 (12.3)
		Women	9	96	60	36	4 (4.2)	39 (40.6)	15	5 (5.2)
	Race	White	116	116	77	50	5 (4.3)	54 (46.6)	17	10 (8.6)
		Asian	2	25	12	11	1 (4.0)	8 (32.0)	3	3 (12.0)
		Other	2	20	11	6	1 (5.0)	6 (30.0)	3	0
All Cancer Population (N = 466)	Age	< 65 years	262	261	155	105	16 (6.1)	100 (38.2)	28	27 (10.3)
		65 to < 75	143	143	91	60	12 (8.4)	75 (52.4)	26	12 (8.4)
		≥ 75 years	6	61	38	29	8 (13.1)	27 (44.3)	16	6 (9.8)
	Sex	Men	257	256	162	117	23 (8.9)	111 (43.2)	37	29 (11.3)
		Women	209	209	122	77	13 (6.2)	91 (43.5)	33	16 (7.7)
	Race	White	318	317	206	137	27 (8.5)	143 (45.0)	49	34 (10.7)
		Asian	5	56	27	24	2 (3.6)	23 (41.1)	6	6 (10.7)
		Other	9	92	51	33	7 (7.6)	36 (39.1)	15	5 (5.4)

Pregnancy, Reproduction and Lactation

Pregnancy

There are no data available on the use of pemigatinib in pregnant women.

Lactation

There are no data on the presence of pemigatinib or its metabolites in human milk, on the effects of pemigatinib on the breastfed child, or on milk production.

Immunological events

According to the study protocol changes in serum immunoglobulin levels or other specific methods to investigate potential immunological events were not performed in the clinical trials. Similarly, the applicant has not provided a discussion of potential immunological events or the impact of pemigatinib on the immunological system.

With respect to the TEAEs of specific interest, there is strong evidence supporting an interference of MAPK pathway with the maintenance of the outer retinal barrier including also phagocytic and immunologic function of the retinal pigment epithelium (Nti et al 2019). However, in the available safety population eye infections were rare (Keratitis n=4). Nevertheless, it should be noted that the TEAE "dry eye", a significant risk for occurrence of infections of the ocular system, was frequently reported.

Safety related to drug-drug interactions and other interactions

For more details regarding DDI please refer to the PK section of this AR

Discontinuation due to adverse events

Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug

In the overall population, among the 13 participants (8.9%) who had TEAEs leading to discontinuation, the only events that occurred in more than 1 participant were intestinal obstruction and acute kidney injury in 2 participants (1.4%) each (seeTable 41: Summary of Treatment-Emergent Adverse Events Leading to Pemigatinib Discontinuation by MedDRA SOC and Preferred Term (Safety **Population)**). Acute kidney injury and hyperbilirubinemia in a single participant each were considered by the investigator to be related to pemigatinib.

Table 41: Summary of Treatment-Emergent Adverse Events Leading to Pemigatinib Discontinuation by MedDRA SOC and Preferred Term (Safety Population)

	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off				
MedDra System Organ Class Preferred Term, n(%)	**Cohort A (N= 107)**	**Cohort B (N= 20)**	**Cohort C (N= 18)**	**Undetermined (N= 1)**	**Total (N=146)**
Participants who had a TEAE leading to discontinuation of pemigatinib	5 (4.7)	3 (15.0)	5 (27.8)	0	13 (8.9)
Gastrointestinal disorders	1 (0.9)	1 (5.0)	1 (5.6)	0	3 (2.1)
Intestinal obstruction	1 (0.9)	1 (5.0)	0	0	2 (1.4)
Gastrointestinal haemorrhage	1 (0.9)	0	0	0	1 (0.7)
Obstruction gastric	0	0	1 (5.6)	0	1 (0.7)
General disorders and administration site conditions	0	1 (5.0)	0	0	1 (0.7)
Performance status decreased	0	1 (5.0)	0	0	1 (0.7)
Hepatobiliary disorders	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Bile duct obstruction	1 (0.9)	0	0	0	1 (0.7)
Cholangitis	0	0	1 (5.6)	0	1 (0.7)
Hyperbilirubinaemia	1 (0.9)	0	0	0	1 (0.7)
Neoplasms benign, malignant and unspecified	0	0	2 (11.1)	0	2 (1.4)
Malignant ascites	0	0	1 (5.6)	0	1 (0.7)
Malignant neoplasm progression	0	0	1 (5.6)	0	1 (0.7)
Nervous system disorders	1 (0.9)	1 (5.0)	0	0	2 (1.4)
Embolic cerebral infarction	0	1 (5.0)	0	0	1 (0.7)
Paraplegia	1 (0.9)	0	0	0	1 (0.7)
Renal and urinary disorders	1 (0.9)	0	1 (5.6)	0	2 (1.4)
Acute kidney injury	1 (0.9)	0	1 (5.6)	0	2 (1.4)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

The TEAE of cholangitis that led to pemigatinib discontinuation was also a serious TEAE with a fatal outcome.

Treatment-Emergent Adverse Events Leading to Interruption of Study Drug

In the overall population, among the 62 participants (42.5%) with TEAEs leading to pemigatinib interruption, the most frequently reported events occurred in the SOC of gastrointestinal disorders (16.4%; see Table 42: Summary of Treatment-Emergent Adverse Events Leading to Pemigatinib Interruption in ≥ 1% of Participants Overall by MedDRA SOC and Preferred Term (**Safety Population)**). By preferred term, the most frequently reported events were stomatitis (7.5%), palmar-plantar erythrodysesthesia syndrome (5.5%), arthralgia (4.8%), and fatigue (4.1%).

Table 42: Summary of Treatment-Emergent Adverse Events Leading to Pemigatinib Interruption in ≥ 1% of Participants Overall by MedDRA SOC and Preferred Term (Safety Population)

	Pemigatinib 13.5 mg QD, 2-weeks-on/1-week-off				
MedDra System Organ Class Preferred Term, n(%)	**Cohort A (N= 107)**	**Cohort B (N= 20)**	**Cohort C (N= 18)**	**Undetermined (N= 1)**	**Total (N=146)**
Participants who had a TEAE leading to pemigatinib dose interruption	47 (43.9)	10 (50.0)	5 (27.8)	0	62 (42.5)
Gastrointestinal disorders	19 (17.8)	3 (15.0)	2 (11.1)	0	24 (16.4)
Stomatitis	10 (9.3)	1 (5.0)	0	0	11 (7.5)
Abdominal pain	3 (2.8)	0	1 (5.6)	0	4 (2.7)
Small intestinal obstruction	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Diarrhoea	2 (1.9)	0	0	0	2 (1.4)
General disorders and administration site conditions	6 (5.6)	4 (20.0)	1 (5.6)	0	11 (7.5)
Fatigue	4 (3.7)	1 (5.0)	1 (5.6)	0	6 (4.1)
Asthenia	1 (0.9)	2 (10.0)	0	0	3 (2.1)
Pyrexia	2 (1.9)	1 (5.0)	0	0	3 (2.1)
Hepatobiliary disorders	5 (4.7)	0	1 (5.6)	0	6 (4.1)
Cholangitis	3 (2.8)	0	0	0	3 (2.1)
Hyperbilirubinaemia	2 (1.9)	0	0	0	2 (1.4)
Investigations	4 (3.7)	2 (10.0)	2 (11.1)	0	8 (5.5)
Alanine aminotransferase	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Aspartate aminotransferase	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Blood alkaline phosphatase	2 (1.9)	0	1 (5.6)	0	3 (2.1)
Electrocardiogram QT prolonged	1 (0.9)	1 (5.0)	0	0	2 (1.4)
Metabolism and nutrition	5 (4.7)	3 (15.0)	0	0	8 (5.5)
Decreased appetite	0	2 (10.0)	0	0	2 (1.4)
Dehydration	2 (1.9)	0	0	0	2 (1.4)
Hypercalcaemia	1 (0.9)	1 (5.0)	0	0	2 (1.4)
Hyperphosphataemia	2 (1.9)	0	0	0	2 (1.4)
Hypophosphataemia	1 (0.9)	1 (5.0)	0	0	2 (1.4)

Musculoskeletal and connective tissue disorders	9 (8.4)	2 (10.0)	1 (5.6)	0	12 (8.2)
Arthralgia	5 (4.7)	2 (10.0)	0	0	7 (4.8)
Back pain	1 (0.9)	0	1(5.6)	0	2 (1.4)
Pain in extremity	2 (1.9)	0	0	0	2 (1.4)
Nervous system disorders	4 (3.7)	0	0	0	4 (2.7)
Syncope	2 (1.9)	0	0	0	2 (1.4)
Renal and urinary disorders	2 (1.9)	1 (5.0)	0	0	3 (2.1)
Acute kidney injury	1 (0.9)	1 (5.0)	0	0	2 (1.4)
Skin and subcutaneous tissue disorders	13(12.1)	1 (5.0)	0	0	14 (9.6)
Palmar-plantar	8 (7.5)	0	0	0	8 (5.5)
Onychomadesis	2 (1.9)	0	0	0	2 (1.4)
Vascular disorders	3 (2.8)	0	0	0	3 (2.1)
Hypotension	2 (1.9)	0	0	0	2 (1.4)

Note: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions; Cohort B = other FGF/FGFR alterations; Cohort C = negative for FGF/FGFR alterations; Undetermined = undetermined FGF/FGFR status.

Treatment-Emergent Adverse Events Leading to Dose Reduction of Study Drug

Treatment-emergent AEs leading to discontinuation of pemigatinib administration for participants were 13/146 (8.9%) in Study INCB 54828-202 and slightly higher with 45/466 (9.7%) in the All Cancer Population. In general, the reasons for discontinuation due to AEs as indicated by the SOCs and PT are consistent with the underlying diseases under study and the known toxicities of pemigatinib. The following Table 43 provides an overview about the TEAEs leading to pemigatinib discontinuation in the three safety populations.

Table 43: Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation in ≥ 2 Participants in Study INCB 54828-202, the Cholangiocarcinoma Population, or the All Cancer Population

MedDRA System Organ Class Preferred Term, n (%)	INCB 54828-202 (N = 146)	Cholangiocarcinoma Population (N = 161)	All Cancer Population (N = 466)
Any TEAE leading to study drug	13 (8.9)	13 (8.1)	45 (9.7)
Gastrointestinal disorders	3 (2.1)	3 (1.9)	9 (1.9)
Intestinal obstruction	2 (1.4)	2 (1.2)	2 (0.4)
Small intestinal obstruction	0	0	2 (0.4)
General disorders and administration site	1 (0.7)	1 (0.6)	6 (1.3)
Disease progression	0	0	2 (0.4)
General physical health deterioration	0	0	2 (0.4)
Infections and infestations	0	0	2 (0.4)
Pneumonia	0	0	2 (0.4)
Metabolism and nutrition disorders	0	1 (0.6)	4 (0.9)
Dehydration	0	1 (0.6)	2 (0.4)
Renal and urinary disorders	2 (1.4)	2 (1.2)	4 (0.9)
Acute kidney injury	2 (1.4)	2 (1.2)	4 (0.9)

Dose interruptions and reductions due to TEAEs occurred in 42.5% and 13.7% of participants in Study INCB 54828-202. The most common events consistent with FGFR inhibition and leading to dose interruption were stomatitis (7.5%), palmar-plantar erythrodysesthesia syndrome (5.5%), and arthralgia (4.8%).

Post marketing experience

On April 17, 2020, the FDA granted accelerated approval to pemigatinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement. However, no postmarketing data are available yet.

2.6.1. Discussion on clinical safety

Overall, a total of 562 participants have been treated with at least one dose of pemigatinib in monotherapy; 484 with advanced malignancies and 78 healthy participants. Further 44 participants in study INCB 54828-101 received at least one dose of pemigatinib in combination. Data are not available for paediatric population due to the extreme rareness of the disease in patients below 18 years of age and this is fully acceptable and captured in the PIP-waiver. Adequate exposure in elderly >75 years is missing, however, since the pivotal trial reflects the age distribution in the orphan disease, cholangiocarcinoma population, this is not a significant concern. As the product has been demonstrated to be teratogenic in animal studies, the product should not be used during pregnancy and lactation (see SmPC section 4.4).

Information related to the overall safety profile of pemigatinib in cholangiocarcinoma came mostly from study INCB 54828-202 (FIGHT-202); safety results of pemigatinib in the claimed indication came only from the cohort A of the same study. Together with these patients from study FIGHT-202, safety results from additional 15 cholangiocarcinoma patients from studies INCB 54828-101 and INCB 54828-102 have been pooled into the 'Cholangiocarcinoma population' (n= 161). To note, patients in the 'Cholangiocarcinoma population' have been exposed to a range of pemigatinib doses from 9 up to 20 mg.

The entire safety database is only based on data from single-arm trials in different diseases.

The median durations of exposure for the Study INCB 54828-202 safety population, the Cholangiocarcinoma Population and the All Cancer Population, were 181.0, 181.0, and 104.0 days, respectively, which seems rather short. In the larger All Cancer Population, which included participants treated with pemigatinib over a dose range of 1 to 20 mg QD on an intermittent or continuous schedule, long-term exposure was even smaller as reflected from the fact that 30.7% of participants received pemigatinib for > 6 months, and 8.6% of participants received pemigatinib for > 12 months. In Study INCB 54828-202, the median exposure in cohort A is 219 days (7, 730) whereas in cohort B and C the exposure is at least 5 times lower; median exposure of 41.5 (7, 393) and 39.4 (7, 142) days for cohort B and C, respectively. The difference in the exposure among the cohorts was due to patients' discontinuation mainly to progressive disease. This might support the idea that the FGFR2 is a good prognosis biomarker. In this sense, it is preferred to assess the safety findings of pemigatinib focusing in the intended population, cohort A, even if data from cohort B and C is considered as supportive.

The number of patients treated in the intended population might be enough to be able to assess the safety profile, however the number of patients being treated for a long time is low and the follow-up is limited.

Considering the doses explored in the target population, appreciable experience is only available for the 13.5 mg dose. Regarding the dose regimen, the applicant has investigated a continuous versus an intermittent administration, particularly for the preferred 13.5 mg QD pemigatinib dose. The intermittent administration of this dose was finally selected for the recommended posology due to a better tolerability compared with the continuous administration. Mainly, the management of hyperphosphataemia as well as of diarrhoea TEAEs and Stomatitis was more favourable with this form of administration according to data. However, an MTD was not defined in the phase I trial, since inhibition of the target molecule was already sufficient at this dose to expect full efficacy.

All participants in Study INCB 54828-202 had at least one TEAE (100%). Generally, TEAEs were most frequently reported in the following SOCs; gastrointestinal disorders, metabolism and nutrition disorder, skin and subcutaneous tissue disorders and general disorders and administration site conditions in the total population of study FIGHT-202; most commonly reported TEAEs were hyperphosphatemia, alopecia, diarrhoea, fatigue, dysgeusia. The **most common TEAEs**, including hyperphosphatemia, alopecia, diarrhoea, fatigue, nail toxicity, dysgeusia, nausea, constipation, stomatitis, dry mouth, decreased appetite, vomiting, dry eye, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin, were consistent with FGFR inhibition and/or an oncology population. The majority of these common events, considered related to pemigatinib by the investigator, were reported as Grade 1 or 2 in severity, nonserious, and did not lead to pemigatinib dose modification. However, treatment-emergent events of ≥ Grade 3 severity occurred in 63.7% of participants in Study INCB 54828-202 and were most commonly (≥ 5%) events of hypophosphatemia, arthralgia, hyponatremia, and stomatitis.

- Focusing on the clinically more relevant TEAEs ≥ grade 3, the most frequently reported events were associated with the SOCs of gastrointestinal disorders (23.3%) and metabolism and nutrition disorders (21.9%)
- Hypophosphatemia (12.3%) was the most common ≥ Grade 3 event

Other ≥ Grade 3 TEAEs that occurred in ≥ 5% of participants in Study INCB 54828-202 include arthralgia, hyponatremia, and stomatitis.

As usual in trials in oncology, it remains sometimes difficult to differentiate definitively between disease- and drug-related AEs. Investigator assessment of causality was also captured. If the investigator did not specify the relationship of the AE to the study drug, then the AE was considered treatment related. This conservative approach seems adequate and explains that nearly all TEAEs (91.5 - 94.5) were classified as drug-related by the investigator.

Nevertheless, the high rates of 41.6 % SAEs and ≥ Grade 3 TEAEs (62.1%) as well as 7/161 (4.3) fatal TEAEs may probably also indicate significantly the underlying disease. This is in line with the finding that only a small proportion of participants in each population had at least one serious event that was considered related to pemigatinib by the investigator (4.1%, 3.7%, and 6.8%, respectively) in trial INCB 54828-202 claimed as pivotal.

Since no comparator data in the intended target population is available, the relation between TEAEs observed and the drug treatment remains uncertain.

Serious TEAEs (including serious events with a fatal outcome) occurred in similar proportions of participants in Study INCB 54828-202 (44.5%) and in the Cholangiocarcinoma and All Cancer Populations (41.6% for

both pooled populations). The most frequently reported events pertain to SOCs Gastrointestinal disorders and Infections and infestations.

TEAEs leading to fatal outcome were reported by a total of 4.1% of the patients; 2.8%, 10.0% and 5.6% of the patients in cohorts A, B and C, respectively. Overall, 6 cases (4.1%) of serious TEAEs from the all patients enrolled led to fatal outcomes; 3 cases in cohort A, 2 cases in cohort B and 1 case in cohort C. These events were classified in SOCs hepatobiliary disorders, infections and infestations, metabolism and nutrition disorders and respiratory, thoracic and mediastinal disorders. The three fatal cases in cohort A were due to bile duct obstruction and failure to thrive.

It is noted that at least one serious TEAE related to pemigatinib was associated with a fatal outcome. This was a cerebrovascular accident in a participant in the All Cancer Population. However, causality assessment for the event was confounded by a concurrent cardiovascular condition (patent foramen ovale), obesity, and hypothyroidism.

Interruption was the main strategy for toxicity management in the study FIGHT-202. **TEAEs leading to dose interruption** were, thus, more frequently reported that TEAEs leading to discontinuation or dose reduction, reported in 42.5% of the total population; 43.9%, 50.0% and 27.8% of the patients in cohorts A, B and C, respectively. The main cause of dose interruption were gastrointestinal disorders. **TEAEs leading to discontinuation** were reported in 8.9% of the total patients; 4.7%, 15.0% and 27.8% of the patients in cohorts A, B and C, respectively. **TEAEs leading to dose reductions** were reported in 13.7% of the patients; 15.9%, 10.0% of the patients in cohorts A, B respectively. None TEAE leading to dose reduction was reported in cohort C. The main cause of dose reductions were skin and subcutaneous tissue events.

AESIs

The incidence of ***nail toxicity*** in study FIGHT-202 in the total population was 42.5%; 52.3% in the cohort A and slightly lower in the All Cancer population (35.0%). The majority of these events were Grade 1 or 2 in severity. None of the event were serious or led to discontinuation. The number of dose interruptions and dose reduction in the total population due to these AEs is relatively low (4.1% and 3.4%, respectively). The estimate of median time to first occurrence of any grade nail toxicity was 5.98 months.

Adverse events regarding the **skin and subcutaneous tissue disorder SOC** were frequent (73.3%) but only rarely ≥3 Grade (5.5%). Most of the events were regarding alopecia (49.3%), but events might have been additionally confounded by previous chemotherapy. Dry skin was observed in 19.9% and may be seen like palmar-plantar erythrodysaesthesia syndrome (16.3%, Grade ≥ 3 events: 4.1%) as clearly drug-related.

Overall, these toxicities seem manageable.

Hyperphosphatemia is an expected effect of FGFR inhibition and non-clinical data confirm the relevance of these events. Hyperphosphatemia has also been associated with pemigatinib and other FGFR inhibitors in clinical trials (Balversa 2019, Hollebecque et al 2018, Necchi et al 2018). Insofar, TEAEs and laboratory findings demonstrating that pemigatinib administration was associated with increases in phosphate levels could be expected. Thus, the study protocols included already recommendations based on serum phosphate levels for managing this on-target effect. Dietary phosphate restriction, administration of phosphate-binding therapy, and increased phosphate monitoring were recommended initially, and a phosphaturic agent could also have been added. If these interventions were insufficient to manage serum phosphate levels while taking pemigatinib, then dose modification (interruption and/or dose reduction) and finally permanent discontinuation of pemigatinib were recommended.

Hyperphosphatemia was observed in 60.3% of the patients in the pivotal trial INCB 54828-202, but only 5 participants with ≥ Grade 3 and/or serious TEAEs of hyperphosphatemia, and a review of cases of seizure and QT prolongation in participants in the All Cancer Population did not suggest a relationship to pemigatinib.

Hypophosphatemia was the most common ≥ Grade 3 TEAE in Study INCB 54828-202 (12.3%) and the Cholangiocarcinoma Population (14.3%) and the second most common ≥ Grade 3 TEAE among participants in the All Cancer Population (6.2%). In study INCB 54828-202, ***hypophosphatemia*** events were reported in 25.2% of the total population; 25.2% in cohort A compared to 20.0% and 11.1% in cohort B and C, respectively. These events were ≥ grade 3 in 12.3% of the total population. None of the events of hypophosphatemia were serious, led to discontinuation, or led to dose reduction. Dose interruption was reported in 1.4% of participants.

However, large proportions of participants in Study INCB 54828-202 (67.8%), the Cholangiocarcinoma Population (68.3%), and the All Cancer Population (47.9%) had treatment-emergent low phosphate values, suggesting a problem in the characterisation of this risk.

The aetiology(ies) for low serum phosphate values are unknown, but a higher incidence of treatment-emergent low phosphate values among participants treated with pemigatinib on an intermittent schedule (52.0% vs 24.3%) suggests that negative feedback (eg, increases in FGF23) and/or procedures used to manage hyperphosphatemia could contribute.

Further, deficiencies in the reported frequencies of this hypophosphatemia and other biological components associated has been found. In the case of lab parameters, AEs are mostly defined per CTAE guidelines as an increase or decrease of the lab value and is graded according to a range of variation with regards to normal limits. In the definition of these type of AEs there is no a clinical perception, just the objective measures of lab values. Notable, there are no correlation in the frequencies reported for AEs and its related lab value for the given parameter; e.g.; hypophosphatemia was reported in 25.2% of the patients from the total population whereas, phosphate decreased was reported in 67.8% of the patients from the total population, calcium increased was reported in 42.5% whereas hypercalcemia was reported in 15.1% of the total population and calcium decreased reported in 17.1% whereas hypocalcaemia was reported in 2.7% of the total population.

Serous retinal detachments and other ocular disorders are directly related to pemigatinib's mechanism of action (FGFR-MAPK signalling) and findings in nonclinical studies of pemigatinib. Serous retinal detachment/central serous chorioretinopathy is frequently **reported for inhibitors of MEKs and MAPKs and is sometimes also referred as MEK inhibitor–associated retinopathy**. The mechanism(s) by which inhibition of MEK and MAPK pathways produces subretinal fluid and how MEK inhibitor–associated retinopathy is different from central serous chorioretinopathy are not fully understood. There is strong evidence supporting an interference of MAPK pathway with the maintenance of the outer retinal barrier and/or phagocytic, immunologic and/or pump function of the retinal pigment epithelium. Inhibition of FGFR may lead to a similar interference with the integrity of the outer retinal barrier and/or function of the retinal pigment epithelium, as FGFR2 is expressed in retina and is important in the function of retinal pigmented epithelial cells. Safety assessments thus, included monitoring for ocular toxicities with visual acuity test, slit-lamp examination, and funduscopy with digital imaging and additional ophthalmologic assessments (eg, OCT) were performed if clinically indicated.

Serous retinal detachment was reported in 4.1% of the total population in Study INCB 54828-202; 3.7% (4/107) in cohort A compared to 5.0% (1/20) and 5.6% (1/18) in cohort B and C. The majority of the events

were Grade 1- 2 in severity. This needs further clarifications as grade 1 events is defined as asymptomatic per CTCAE v4.03 and no routine ophthalmological examination were defined in the CTP.

Serous retinal detachment or detachment of retinal pigment epithelium occurred in 5.6%, and 7.5% of participants in the Cholangiocarcinoma Population, and the All Cancer Population, respectively. Overall, three patients had ≥ grade 3 events; one of these was classified as non-related. Serous retinal detachment events were only rarely responsible as reflected by the low incidences of events leading to pemigatinib dose interruption (0.6% - 1.7%), dose reduction (0% - 0.4%) and drug discontinuation (0% - 0.4%) across the three populations.

Further, the most common TEAEs reported under the **SOC eye disorders** was dry eye, reported in 25.3% of the total population and in 31.8% of the patients in cohort A. In cohort B and C the reported frequency was lower, 5.0% and 5.6%, respectively. Other events under eye disorders of relevance that were reported in ≤5% in patients of cohort A are blepharitis (4.7%), eye pain (4.7%), vitreous floaters (3.7%), cataract (3.7%), vision blurred (3.7%), keratitis (2.8%), visual impairment (2.8%) and vitreous detachment (2.8%). Information on section 4.8 of the SmPC has been included on all these events.

Renal impairment - In the non-clinical results in primate, the animals had very frequently renal lesions, characterised by a constellation of changes that included multifocal, reactive hyperplasia/hypertrophy of proximal and collecting tubular epithelium, subacute-to-granulomatous proliferative renal tubular inflammation, diffuse renal tubular degeneration and necrosis, and renal tubular mineralisation 30 to 60 % of the animals (n=female 2/6 vs male 4/6). These changes occurred at a significantly higher dose of 3 mg/kg/day, that are >2.0-fold the clinical exposure at 13.5 mg; no renal findings were observed at exposures 0.5-fold human exposure for up to 90 days. The observed renal findings were considered unrelated to morbidity observed in animals at this same dose. At this point, it is considered that the safety data from patients administered doses up to 13.5mg (unbound AUC 0.25 uM) in clinical trials are more relevant to understanding potential renal liabilities in patients.
This might be correct, and the nature of the renal ADRs observed in patients may calls into question the relevance of the monkey data to human experience since ≥ Grade 3 TEAEs of blood creatinine increased and/or acute kidney injury occurred in 4 participants with renal impairment at baseline.
However, one of the serious TEAEs of acute kidney injury was considered related to pemigatinib; the other events of blood creatinine increased/acute kidney injury were considered unrelated to pemigatinib by the investigator. None of these events were fatal.
Considering that - beside identified TEAE of special interest - identification of drug relationship of adverse events observed in an advance cancer population is always a challenge due to overlapping disease symptoms and even most cases of death are nearly exclusively imputed to disease progression, the non-clinical signals remain an open safety concern. In particular, since a clear explanation for the primate morbidity could not be identified. Nevertheless, it is agreed that from the limited data available the currently known toxicity seems not to be very pronounced or intolerable in principle, although the full consequences of some of the adverse events remains uncertain. Moreover, it is noted that additional controlled and thus, probably more reliable safety data can be expected from the started phase III trial in the first line setting.

Safety in special populations:

Demographic covariates, including age, weight, BMI, gender, and race, were explored to assess their effect on the PK of pemigatinib in the population PK analysis. However, in the small population of

Cholangiocarcinoma patients available interpretation of the safety differences regarding adverse events reported from subgroup analyses can be only interpreted with caution, as usual in other applications for orphan diseases. In general, it seems difficult to identify robust signals from this data source. Subgroup analyses in the larger All cancer population seems to be biased by other underlying diseases and thus, less reliable.
Therefore, potential differences of safety profiles in special populations is scarcely characterised in this application due to the limited number of patients included in the clinical trial in cholangiocarcinoma patients. Since the cholangiocarcinoma population consists only of 164 patients, interpretation of this data remains preliminary and uncertain. Although differences in the incidences TEAEs occurred, consistent patterns suggestive of meaningful differences in the safety profile of pemigatinib for these demographic subgroups were not observed. From the available data, no additional safety concerns for pemigatinib were identified for participants in a particular age, race, or sex subgroup. However, imbalances at baseline, which may represent the disease characteristic (age and sex), may have biased additionally the outcome.

There are no data available on the use of pemigatinib in **pregnant women**. However, based on findings in animals and its mechanism of action, pemigatinib may cause foetal harm when administered to pregnant women.

There are no data on the presence of pemigatinib or its metabolites in **human milk**, the effects of pemigatinib on the breastfed child, or on milk production.

Immunological events:

According to the study protocol changes in serum immunoglobulin levels or other specific methods to investigate potential immunological events were not performed during the clinical development of pemigatinib. Most participants had normal vital signs measurements at baseline and at all-time points assessed. Changes were generally small, and no clinically meaningful trends were observed.

Additional expert consultations

The scientific advisory group (SAG) consulted in the frame of Pemazyre assessment provided the following view:

The safety profile was overall agreed to be manageable and the toxicity tolerable provided adequate dose reductions as recommended in the SmPC. Specific issues identified, such as retinal detachment, although rare and transient should be adequately addressed in the risk management plan.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Additional safety data needed in the context of a conditional MA

Limitations in the safety assessment are still present. Insofar, significant uncertainty remains. However, it is noted that additional, controlled and thus, more safety data can be expected from the started phase III trial in the first line setting. Although this is a different population, it might help to answer the currently open questions at the end.

2.6.2. Conclusions on the clinical safety

Pemigatinib showed a non-negligible safety profile with high incidence and high level of seriousness of the events reported, mainly related to metabolic disorders, gastrointestinal disorders and skin and subcutaneous tissue disorders. Main safety concerns are related to the deficiencies in the characterisation of important identified risks as serous retinal detachments and hyperphosphatemia, together with other serious ocular events and metabolic alterations. Risks from pemigatinib's toxicities in the applied population can be summarised as clinically relevant.

Nevertheless, the safety profile of pemigatinib monotherapy appears sufficiently characterised at this stage and risk minimisation measures have been implemented. Additional data from ongoing studies are expected to be provided in support of the overall safety.

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

- In order to confirm the efficacy and safety of Pemazyre in adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy, the MAH should submit the final results of study FIGHT-202 (INCB 54828-202), a phase 2 study investigating the efficacy and safety of pemigatinib in adults with advanced/metastatic or surgically unresectable cholangiocarcinoma including FGFR2 translocations who failed previous therapy. The CSR should be submitted by 31 December 2021.
- In order to confirm the efficacy and safety of Pemazyre in adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy, the MAH should submit the results of FIGHT-302 (INCB 54828-302), a phase 3 study comparing the efficacy and safety of pemigatinib vs. gemcitabine plus cisplatin chemotherapy in adults with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement. The CSR should be submitted by 31 December 2026.

2.7. Risk Management Plan

Safety concerns

Table 44: Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Serous retinal detachment Hyperphosphatemia
Important potential risks	Embryo-foetal toxicity Acute kidney injury
Missing information	None

Pharmacovigilance plan

There are currently no additional pharmacovigilance activities for pemigatinib.

Risk minimisation measures

Table 45: Summary Table of Risk Minimisation Activities by Safety Concern

Safety concern	**Risk minimisation measure**
Serous retinal detachment	Routine risk minimisation measures: • SmPC section 4.4 • SmPC section 4.8 • Package Leaflet section 2
Hyperphosphatemia	Routine risk minimisation measures: • SmPC section 4.4 • SmPC section 4.8 • Package Leaflet section 2
Embryo-foetal toxicity	Routine risk minimisation measures: • SmPC section 4.4 • SmPC section 4.6 • Package Leaflet section 2
Acute kidney injury	Routine risk minimisation measures: • SmPC section 4.4 • SmPC section 4.8 (Blood creatinine increased)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17th April 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of pemigatinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers pemigatinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Pemazyre (pemigatinib) is included in the additional monitoring list as

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU <include reason(s)
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

3.1.2. Available therapies and unmet medical need

Currently, there is no consensus regarding the optimal treatment modality for locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement in the second line treatment setting and beyond. Several treatments, including multi-agent chemotherapy regimens, radiation and surgery, are generally used to treat patients. For the majority of patients the only treatment option from the second line setting seems to be systemic chemotherapy or palliative treatment depending on the performance status.

Achievement of high rates of durable response with a FGFR-targeted therapy in patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement and relapsing or refractory after at least one line of systemic therapy, while avoiding the morbidity and mortality observed with chemotherapy regimens it is potentially very impactful in this disease.

CCA with FGFR genetic alterations seems to reflect a distinct clinical phenotype with a better prognosis.

3.1.3. Main clinical studies

The main data of efficacy of pemigatinib in patients with locally advanced/metastatic or surgically unresectable CCA with a FGFR2 fusion or rearrangement are derived from study INCB 54828-202 (FIGHT-202). This was a prospective, open-label, single-arm, multinational study initiated in January 2017 evaluating the efficacy and safety of pemigatinib in participants with advanced/metastatic or surgically unresectable CCA with FGFR2 fusion or rearrangement who have progressed on at least 1 line of prior systemic therapy.

3.2. Favourable effects

As of the data cutoff date (22 March 2019), out of the 107 subjects enrolled in Cohort A (Efficacy Evaluable Population), after a median follow up of 15.44 months (min, max: 7.0 to 24.7 months), a total of three subjects had a confirmed CR (2.8%) and 35 subjects had a confirmed PR (32.7%) which results in ORR of 35.5% (95% CI: 26.50, 45.35) as assessed by IRC. The study achieved the threshold predetermined by the applicant for a positive outcome (lower limit of the 95% CI for ORR > 15%). The sensitivity analysis of ORR in the PP population (n = 104) was consistent with an ORR of 35.6% (95% CI: 26.43, 45.57), including three CR (2.9%) and 34 PR (32.7%).

Among the 38 participants in Cohort A with IRC-assessed confirmed tumour responses, median DOR was 7.49 months (95% CI: 5.65, 14.49). Among the three patients with confirmed CR, the duration of response was long for one patient (19.52 months), but for the other two the duration of response was relatively short (4.83 and 6.34 months).

Fifty patients had SD as a best response (46.7%) maintained for a minimum of 39 days since first pemigatinib dose, which results in a DCR of 82.2% based on IRC assessment.

The median PFS based on IRC assessment was estimated at 6.93 months (95% CI: 6.18, 9.59) and the median OS was 21.06 months (95% CI: 14.82, NE).

Median time to response in the 38 participants in Cohort A with IRC-assessed, confirmed tumour responses was 2.69 months (range: 0.7-6.9 months) and 60.7% (65/107) of participants had a duration of pemigatinib treatment > 6 months.

In order to provide updated data on efficacy and more matured survival data, the applicant conducted another data cut on 07 April 2020. With a median time to follow-up of 27.91 months for Cohort A patients at the time of this data cut, 10 (9.3%) patients in Cohort A were still on treatment and 98 (90.7%) had discontinued, mostly due to progressive disease (67.6%). The ORR was 37% (95% CI: 27.94, 46.86) based on confirmed responses by an IRC. Four participants (3.7%) had complete responses and 36 participants (33.3%) had partial responses. Median DOR was 8.08 months (95% CI: 5.65, 13.14). Observed DOR was at least 6 months in 23 responders (57.5%), at least 9 months in 15 responders (37.5%), and at least 12 months in 10 responders. Efficacy data are therefore confirmed and even slightly reinforced.

3.3. Uncertainties and limitations about favourable effects

CCA is a very heterogeneous population and according to the literature it was reported that patients with CCA with FGFR genetic aberrations (GAs) have a distinct clinical phenotype with a better prognosis than patients without FGFR GAs (Jain et al, 2018). Nevertheless, FGFR alterations have been identified as potential markers for target therapies. However, the contribution of these genetic changes to cholangiocarcinoma genesis and the relevance of a targeted therapy against these mutations remains unknown. There were no IRC-assessed, confirmed tumour responses in Cohort B (20 participants with other FGF/FGFR alterations) or in Cohort C (18 participants with tumours negative for FGF/FGFR alterations), demonstrating that pemigatinib is a targeted therapy with marked activity against the target: FGFR2-rearranged cholangiocarcinoma. Since from the mode of action and the IC 50 pemigatinib concentrations should also act against FGF/FGFR 1 and 3 alterations, the absence of any change in tumour volume in these entities would suggest that the ORR observed in FGFR2 alterations may not be caused by the treatment alone to which in any case contributes. Furthermore, the lack of robust historical data for this sub-population, and even more in the second line treatment setting and beyond where the impact of FGFR2 inhibition in terms of clinical outcome remains unknown, and in the absence of propensity score matching analyses submitted, it is difficult to provide a clear interpretation of the efficacy results and contextualise the effect observed. In this context, results from the studies performed by the applicant can be considered highly valuable in order to contextualise data. Based on the above, the proposed prospective Phase 3 randomised controlled trial (INCB 54828-302), in the context of the conditional Marketing authorisation, will allow to further assess a potential survival benefit in this subpopulation from FGFR inhibitors (as pemigatinib).

The frequencies of intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) among the population of the study FIGHT-202 are consistent with the literature in which the majority of FGFR2 fusion or rearrangement is observed in ICC. The results observed both in terms of response and survival are thus mainly based on the results from the sub-population of ICC. Too few patients with ECC received pemigatinib in the study FIGHT-202 and considering that CCA is a very heterogeneous population, it might be difficult to determine the treatment benefit in ECC sub-population.

Finally, only non-clinical preliminary data for the characterisation of the pharmacological profile of pemigatinib have been provided with a lack of raw data. More data from the proposed confirmatory study are considered crucial to underline the potency and activity of pemigatinib for the proposed indication.

The final study report with an updated data from the on-going INCB 54828-202 and the randomised phase 3 studies (INCB 54828-302) to be submitted post approval will address the above reported uncertainties.

3.4. Unfavourable effects

The total safety database consists of 562 patients. The entire safety database is only based on data from single-arm trials in different diseases. A total of 146 patients with cholangiocarcinoma have been exposed to pemigatinib in study INCB 54828-202 (FIGHT-202). The safety results of pemigatinib in the claimed indication came only from 107 patients in the cohort A of the same study.

Most common (≥20%) TEAEs in patients from cohort A were alopecia (58.9%), hyperphosphatemia (55.1%), diarrhoea (52.3%), dysgeusia (47.7%) and fatigue (44.9%), nausea (40.2%), constipation (40.2%), stomatitis (38.3%), dry mouth (38.3%), dry eye (31.8%), vomiting (30.8%), decreased appetite (29.9%), arthralgia (29.0%), dry skin (25.2%), hypophosphataemia (24.3%), pain in extremity (23.4%), back pain (22.4%) and abdominal pain (22.4%).

Overall, 63.7% (93/146) of the all patients enrolled in study FIGHT-202 reported a ≥ Grade 3 TEAE; 59.8% (64/107) of the patients in Cohort A. TEAEs ≥ Grade 3 were most frequently reported in the SOCs gastrointestinal disorders and metabolism and nutrition disorders. The most common reported TEAEs ≥ Grade 3 (>5%) in patients from cohort A were hypophosphataemia (12.1%), stomatitis (7.5%), arthralgia (6.5%) and palmar-plantar erythrodysaesthesia (5.6%).

Serious TEAES were reported in 44.5% (65/146) of all the enrolled patients of study FIGHT-202; 40.2% in cohort A. The most frequently reported events (>10%) in the total enrolled population pertaining to SOCs gastrointestinal disorders and infections and infestations. The most frequently reported SAEs (>2%) in cohort A were pyrexia (4.7%), abdominal pain (3.7%), cholangitis (3.7%) and cholangitis infective (2.8%).

TEAEs leading to fatal outcome were reported by a total of 4.1% of the patients; 2.8% in cohort A. The three fatal cases in cohort A were due to bile duct obstruction and failure to thrive. TEAEs leading to dose interruption were more frequently reported than TEAEs leading to discontinuation or dose reduction, reported in 42.5% of the total population; 43.9% of the patients in cohort A. TEAEs leading to discontinuation were reported in 8.9% of the total patients; 4.7% in cohort A. TEAEs leading to dose reductions were reported in 13.7% of the patients; 15.9% in cohort A. The main cause of dose reductions were skin and subcutaneous tissue events.

Events as *nail toxicity*, *hyperphosphatemia*, *hypophosphatemia* and *serous retinal detachment* were considered as AESIs. Other events of interest under the SOC eye disorders were: dry eye, blepharitis, eye pain, vitreous floaters, cataract, vision blurred, keratitis, visual impairment or vitreous detachment.

From a non-clinical point of view and regarding the data provided by the applicant and the results of the toxicological studies, significant warnings were added in 4.4 of the SmPC with respect to soft tissue mineralisation, ophthalmic findings and nephrotoxicity. These effects observed during non-clinical studies are likely to occur in humans and should be monitored appropriately.

3.5. Uncertainties and limitations about unfavourable effects

In the small population of cholangiocarcinoma patients available, interpretation of the safety differences regarding adverse events reported from subgroup analyses can be only interpreted with caution, as usual in other applications for orphan diseases. In general, it seems difficult to identify robust signals from this data source and safety in special groups of patients is not sufficiently defined.

Entire safety database is based on data from single-arm trials in different diseases. In this context, the causality of the adverse events is difficult to demonstrate as they can be due to the drug effect, disease, aging or other factors. Further, adverse events overlapping with signs from the disease as events in SOCs gastrointestinal disorders and metabolism and nutrition disorders where highly reported in study FIGHT 202. Thus, weighing the safety profile of pemigatinib against other chemotherapy treatments currently used for treatment of cholangiocarcinoma is difficult.

The most important uncertainties about the unfavourable effects are related to risk of serous retinal detachment and hyperphosphatemia (also confirmed during non-clinical studies). Serous retinal detachment has been classified as important potential risk in the RMP and routine PhV measures have been proposed. However, the severity of the risk as reported seemed to have been underestimated and there is not enough information related to the outcome, recurrence, management strategy or the effectiveness of the preventive measures proposed for this event. Indeed, this event seemed to be asymptomatic or mild so first signs and symptoms that could alert of developing this event are unknown. Additional ocular events have also been reported at relatively high frequency whose consequences on the long term were not characterised. Dry eye contributes to the "sicca"-symptomatic during treatment with pemigatinib and is a significant risk for occurrence of infections of the ocular system, which was a frequently reported TEAE. Ocular toxicity has also been identified in non-clinical studies. Findings do not seem to be reversible and no safety margin in regard to the possible clinical relevance was presented by the applicant. The unclear underlying mechanism for the observed changes raises however some uncertainties about the clinical risks at short and long-term.

Hyperphosphatemia has been included as important potential risk in the RMP and routine PhV measures have been proposed. Hyperphosphatemia could be expected with the use of pemigatinib due to its pharmacological effect of FGFR inhibition. However, the contrary effect was reported at higher frequency and seriousness. The effectiveness of management actions and preventive measures have been called into question. Additionally, deficiencies have been found calling into question also the reported frequencies for this type of event. Abnormal laboratory values for calcium, vitamin D, sodium (hyponatraemia) and PTH were also reported and also inconsistencies in the reporting frequencies were found that need further justification or, even a reanalysis. Clinical consequences of this metabolic dysregulation both at short and long-term is still unknown.

Renal lesion findings in non-clinical studies in primate, even though occurring at a significantly higher dose of 3 mg/kg/day than the therapeutic one, are still considered a concern therefore the issue of renal safety needs further clarification.

The mechanism behind the risk for palmar-plantar erythrodysaesthesia syndrome (16.3%, Grade ≥ 3 events: 4.1%) remains not comprehensible and should be explained in the context of the disease, since this adverse event was obviously significantly more frequent in the Cholangiocarcinoma population.

According to the study protocol changes in serum immunoglobulin levels or other specific methods to investigate potential immunological events were not performed during the clinical development of pemigatinib.

The relatively short follow-up time is a limitation to discern potential long-term effects of pemigatinib. Long term safety is insufficiently characterised since median durations of exposure for the cholangiocarcinoma population (181 days) as well as in the All Cancer Population (104 day) was rather short. This concern is also reflected by the fact that only 48.6% of the patients received pemigatinib for > 6 months, and 15.8% received pemigatinib for > 12 months. Insofar, long-term safety remains missing and rare events are not adequately characterised.

The final study report with an updated data from the on-going INCB 54828-202 and the randomised phase 3 studies (INCB 54828-302) to be submitted post approval will address these uncertainties.

3.6. Effects Table

Table 44: Effects Table for pemigatinib in patients with advanced/metastatic or surgically unresectable CCA with FGFR2 fusion or rearrangement (data cut-off: 7 April 2020)

Effect	Short Description	Unit	Pemigatinib	Control	Uncertainties/ Strength of evidence	References
Favourable Effects[a]						
ORR	CR+PR by IRC (primary)	N (%) (95% CI)	40 (37.0) (27.94, 46.86)	N/A	SAT	
Median DOR	Time from CR/PR to progression (secondary)	Months (95% CI)	8.08 (5.65, 13.14)	N/A	SAT	
Unfavourable Effects[b]						
TEAEs	regardless causality	%	100	N/A		
TEAEs Grade ≥ 3	regardless causality	%	63.7	N/A		
Serious AEs	regardless causality	%	44.5	N/A		
TEAEs leading to discontinuation	regardless causality	%	8.9	N/A		

Effect	Short Description	Unit	Pemigatinib	Control	Uncertainties/ Strength of evidence	References
TEAEs leading to reduction	regardless causality	%	13.7	N/A		
TEAEs leading to interruption	regardless causality	%	42.5	N/A		
TEAEs leading to death	regardless causality	%	4.1	N/A		

a. Cohort A; b. Total population

Abbreviations: AE: adverse event; TEAE: Treatment-Emergent Adverse Events. ORR: Overall response rate, DOR: Duration of response, PFS: Progression free survival, OS: overall survival.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The use of the pemigatinib as a single-agent therapy provides a clinically meaningful anti-tumour activity. The ORR of 37% is higher compared to currently used therapies (e.g. gemcitabine-based combination therapy, and taxanes-based combination therapy). This antitumour activity is durable as the median duration of response was 8.08 months (95% CI: 5.65, 13.14). This benefit in this last line of treatment is considered clinically relevant. Although the observed durable response is considered a clinical benefit, there is a need to further confirm the efficacy of pemigatinib in a comparative trial (see Annex II of the SmPC). As a conclusion, fulfilment of an unmet medical need could be agreed, and even if patients with FGFR2-driven disease seem to show better prognosis in the second line setting than patients without FGFR2-driven cholangiocarcinoma, the updated ORR of 37% together with the complete response rate, even modest, are clearly higher in comparison with what could be observed with currently used therapies

The safety profile of pemigatinib is non-negligible showing a complex profile with high incidence and high level of seriousness of the events reported, mainly related to metabolic disorders, gastrointestinal disorders and skin and subcutaneous tissue disorders. Main safety concerns are related to the deficiencies in the characterisation of important identified risks as serous retinal detachments and hyperphosphatemia, together with other serious ocular events and metabolic alteration. Nevertheless, the safety profile of pemigatinib monotherapy appears sufficiently characterised and risk minimisation measures have been implemented. Additional data from ongoing studies are expected to be provided in support of the overall safety (see Annex II of the SmPC).

3.7.2. Balance of benefits and risks

The treatment effect of pemigatinib is considered clinically relevant and has been demonstrated in the single pivotal study that was submitted. Treatment appears to be tolerated when adverse effects are closely monitored and actively managed.

Uncertainties are still present due to the lack of direct controls and there is a need for further characterisation of the safety profile. These will be addressed by the studies imposed as specific obligations, which will provide comprehensive data on both efficacy and safety aspects.

Therefore, the benefit-risk balance for Pemazyre in the proposed indication is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

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

Efficacy has been established on the basis of durable ORR in a single-arm trial. Although the durable response is considered a clinically meaningful benefit, there is a need to further quantify the efficacy of pemigatinib in a comparative trial. Study INCB 54828-302, a phase III study to evaluate the efficacy and safety of pemigatinib compared with gemcitabine plus cisplatin in the first-line treatment of participants with FGFR2-rearranged cholangiocarcinoma is ongoing. Single arm study setting also impairs the causality assessment of several key unfavourable effects leading to remaining uncertainties. These could be addressed by the proposed randomised study with gemcitabine plus cisplatin as comparator since it would allow comparisons of both efficacy and safety. The proposed number of patients (approximately 432 participants) would allow a more comprehensive analysis of both favourable and unfavourable effects. As of 15 DEC 2020, the study has 162 sites open to enrolment, with 1039 participants prescreened for the presence of FGFR2 fusions or rearrangements and 36 participants randomised. Based on the above, the CHMP considered that study INCB 54828-302 is likely to provide comprehensive data suitable to confirm the positive benefit-risk balance of Pemazyre.
In addition, the CHMP considered that the MAH should submit the final CSR of the ongoing pivotal study FIGHT 202 investigating efficacy and safety of pemigatinib in adults with advanced/metastatic or surgically unresectable cholangiocarcinoma including FGFR2 translocations who failed previous therapy which will also provide additional comprehensive data to confirm the positive benefit-risk balance of Pemazyre.

- Unmet medical needs will be fulfilled

Pemazyre fulfils an unmet medical need, as locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy is a condition where no treatments are approved in the EU.

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

In view of the fact that no treatments are approved in the EU in this orphan indication, the immediate availability of Pemazyre on the market outweighs the risk inherent in the fact that additional data are still required.

3.8. Conclusions

The overall B/R of Pemazyre (pemigatinib) in the intended indication is positive in the frame of a conditional marketing authorisation.

Divergent positions are appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Pemazyre is favourable in the following indication:

Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within

6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of Pemazyre in adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy, the MAH should submit the final results of study FIGHT-202 (INCB 54828-202), a phase 2 study investigating the efficacy and safety of pemigatinib in adults with advanced/metastatic or surgically unresectable cholangiocarcinoma including FGFR2 translocations who failed previous therapy.	December 2021
In order to confirm the efficacy and safety of Pemazyre in adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy, the MAH should submit the results of FIGHT-302 (INCB 54828-302), a phase 3 study comparing the efficacy and safety of pemigatinib vs. gemcitabine plus cisplatin chemotherapy in adults with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement.	December 2026

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Divergent positions to the majority recommendation are appended to this report.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that pemigatinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Appendix

1. Divergent positions to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 28 Jan 2021 and re-adopted unchanged during revision of opinion on 25 February 2021

DIVERGENT POSITION DATED 28 Jan 2020

Pemazyre EMEA/H/C/005266/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Pemazyre (Pemigatinib) for the following indication:

Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.

The reasons for the divergent opinion are as follows:

The evidence for efficacy of Pemigatinib based on the single arm trial INCB 54828-202 is considered insufficient.

- The overall response rate (ORR) in patients with FGFR2 rearrangement or fusion (Cohort A) (37.0%; 95% CI: 27.94, 46.86), associated with a very low rate of complete response (3.7%), and the duration of response (DoR) (8.08 months; 95% CI: 5.65, 13.14) are unconvincing and not outstanding as would be required for a single-arm trial.
- In the absence of an outstanding ORR and DoR, time-related endpoints would have been needed to establish clinical benefit, but the data on Cohort B and C are inappropriate comparators for estimating the treatment effect of pemigatinib on overall survival (OS) of Cohort A because FGFR2 alterations appear to reflect a distinct clinical phenotype with a better prognosis and prolonged overall survival. In the absence of an appropriate comparator, the impact of treatment with Pemigatinib on OS in Cohort A cannot be reliably estimated. Thus, OS results remain descriptive and non-inferential.

Thus, due to major uncertainties regarding efficacy combined with considerable toxicity of Pemigatinib, we cannot conclude on a positive B/R. In addition, the targeted reporting date of the specific obligation in Dec 2026 or even later is not acceptable.

CHMP Members expressing a divergent opinion:

Martina Weise

Armando Genazzani