22 April 2022
EMA/272390/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tabrecta

International non-proprietary name: capmatinib

Procedure No. EMEA/H/C/004845/0000

Note

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

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List of abbreviations

ADME	Absorption, distribution, metabolism excretion
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AO	aldehyde oxidase
AST	aspartate aminotransferase
ATP	Adenosine triphosphate
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics classification system
BIRC	Blinded Independent Review Committee
BOR	best overall response
CDx	companion diagnostics
CFU	Colony Forming Units
CGDB	Clinico-Genomic Database
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	complete response
CRS	case retrieval strategy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCO	data cut-off date
DCR	disease control rate
DDI	drug-drug interaction
DLT	Dose-limiting toxicity
DILI	drug induced liver injury
DOR	duration of response
DoE	Design of experiments
EC	European Commission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FAS	full analysis set
FCT	film coated tablet
FDA	Food and Drug Administration
FMEA	Failure mode effects analysis
FFPE	formalin-fixed, paraffin-embedded

FISH	fluorescence in situ hybridization
FRC	Functionality-related characteristics
GC	Gas Chromatography
GCN	gene copy number
GGT	gamma-glutamyltransferase
HGF	hepatocyte growth factor
HLGT	high level group term (MedDRA)
HLT	high level term (MedDRA)
HPLC	High performance liquid chromatography
ICI	immune checkpoint inhibitor
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ILD	interstitial lung disease
IPC	In-process control
IR	Infrared
KF	Karl Fischer titration
LFT	liver function test
MAA	marketing authorization application
MATE1	Multidrug and toxin extrusion proteins-1
MATE2k	Multidrug and toxin extrusion proteins-2k
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition
METex14	MET exon 14 skipping mutation
MHLW	Ministry of Health, Labour and Welfare of Japan
MRI	magnetic resonance imaging
MO	Major Objection
MS	Mass Spectrometry
NAS	New active substance
NCCN	National Comprehensive Cancer Network
NE	not estimable
NGS	next-generation sequencing
NIRS	Near Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
NMQ	Novartis MedDRA query
NSCLC	non-small cell lung cancer
OATP	Organic anion-transporting polypeptide
ORR	overall response rate
OS	overall survival
PACMP	Post-approval change management protocol
PAT	Process Analytical Technology
PCTFE	Polychlorotrifluoroethylene
PD	progressive disease
PDE	Permitted Daily Exposure
PD-1	programmed death-1
PD-L1	programmed death-ligand – 1
PE	Polyethylene

PFS	progression-free survival
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PPI	proton-pump inhibitor
PR	partial response
PRO	patient-reported outcome
PT	preferred term
PS	performance status
PSM	propensity score matching
PVC	Polyvinyl chloride
QbD	Quality by design
QLQ	quality of life questionnaire
QTPP	Quality target product profile
RDI	relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
RH	Relative Humidity
RP2D	recommended Phase II dose
RT-PCR	reverse transcription polymerase chain reaction
RWE	real-world evidence
SA	scientific advice
SAE	serious adverse event
SD	stable disease
SMQ	standard MedDRA query
SmPC	Summary of Product Characteristics
SOC	system organ class
TAMC	Total Aerobic Microbial Count
TCGA	The Cancer Genome Atlas Research Network
TKI	tyrosine kinase inhibitor
TPS	tumour proportion score
TTR	time to response
TYMC	Total Combined Yeasts/Moulds Count
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
ULN	upper limit of normal
UV	Ultraviolet
wt	wild-type
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 15 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Tabrecta, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 May 2017

The applicant applied for the following indication:

"Tabrecta is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a mesenchymal-epithelial transition (MET) exon 14 skipping mutation."

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0305/2017 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did 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.

1.5. applicant's request for consideration

1.5.1. Accelerated assessment

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

1.5.2. New active Substance status

The applicant requested the active substance capmatinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a

medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
18/12/2014	EMEA/H/SA/2973/1/2014/I	Paolo Foggi and Kolbeinn Gudmundsson
17/10/2019	EMEA/H/SA/2973/2/2019/II	Serena Marchetti and Paolo Foggi

The scientific advice pertained to the following quality, and clinical aspects:

- The choice of starting materials;
- The use of an external control arm to support the benefit-risk assessment of capmatinib in study A2201;
- The proposed strategy to submit the study A2201 results, together with supportive data from a RWE study X2401, to support a MAA in MET mutated NSCLC.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: Paula Boudewina van Hennik

The application was received by the EMA on	15 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2021
The CHMP Co-Rapporteur's critique on the Assessment Report was circulated to all CHMP and PRAC members on	23 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 September 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	04 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 January

The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	27 January 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 March 2022
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tabrecta on	22 April 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	22 April 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The sough indication is: Tabrecta is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a mesenchymal-epithelial transition (MET) exon 14 skipping mutation.

The term MET-mutated (METmut) is used to denote to patients with tumours harbouring METex14.

2.1.2. Epidemiology

Lung cancer has been one of the most common cancers in the world for several decades. NSCLC accounts for approximately 85% of all lung cancer cases (Francisci et al 2015) and is the most common cause of cancer-related deaths worldwide (approximately 1.8 million in 2020) (WHO - IARC - World Fact Sheets 2020). In Europe, lung cancer is the leading cause of cancer related deaths, responsible for approximately 384000 deaths in 2020, or about 20% of cancer deaths (WHO - IARC - Europe Fact Sheets 2020). The majority of NSCLC patients are initially diagnosed (de novo) with locally advanced or metastatic disease and are therefore not candidates for potentially curative surgery (Nguyen et al 2012).

The METex14 mutation is recognized as an oncogenic driver in advanced NSCLC. It is reported as a rare alteration accounting for approximately 2-4% of NSCLC and usually occurs independently of other molecular drivers (TCGA 2014, Frampton et al 2015, Schrock et al 2016).

2.1.3. Biologic features

MET exon 14 (METex14) skipping alterations leads to a truncated MET receptor lacking the exon 14 encoded sequences. Deletion (i.e., skipping of exon 14) results in oncogenic activation of MET by expression of a truncated receptor with increased stability, as well as augmented and prolonged signalling capability, seemingly turning MET into an oncogenic driver (Cortot 2017).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

It has been two decades since overexpression of the MET protein was observed in tumours and correlated with poor outcomes in several cancer types. Accumulating evidence support that MET dysregulation (METex14 and MET amplification) is also considered a poor prognosis factor; in a retrospective analysis (Vuong et al 2018) pooled results showed that the presence of METex14 in NSCLC patients confers a worse prognosis based on OS (HR 1.82; 95% CI: 1.04, 3.19; p=0.04) compared with NSCLC without the MET mutation. Similarly, in a retrospective, multi-variate analysis, Tong et al (2016) reported that, in addition to age (P<0.001), METex14 and high-level MET amplification were both found to be independent poor prognostic factors in NSCLC patients based on OS (HR 2.156; 95% CI: 1.096,4.242; p=0.026 for METex14 and HR 3.444; 95%CI: 1.398,8.482; p=0.007 for MET amp, respectively). Furthermore, it is reported that MET mutation is independently associated with a distinct and more aggressive clinicopathological phenotype compared to other NSCLC pathologies (Yeung et al 2015, Vuong et al 2018).

2.1.5. Management

The treatment of patients with advanced unresectable NSCLC (Stage IIIB/C) is generally analogous to the treatment of patients with metastatic (Stage IV) NSCLC. In the EU, targeted therapy is available for the most common gene driver mutations associated with NSCLC (e.g. ALK gene rearrangements, ROS1 rearrangements, sensitizing EGFR mutations and BRAF V600E point mutations, NTRK and RET gene fusion). The currently approved treatment options in the EU that cover NSCLC with METex14, i.e. advanced NSCLC with no established molecular driver (or with no available targeted therapy for known oncogenic drivers, i.e. unselected NSCLC), are now routinely based on immune checkpoint inhibitors (ICIs) and/or chemotherapy.

On 16 February 2022, Tepmetko was authorised in the EU for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy

2.2. About the product

Capmatinib (INC280) is an orally bioavailable, small molecular inhibitor of MET receptor tyrosine kinase. Capmatinib inhibits MET phosphorylation (both autophosphorylation and phosphorylation triggered by the ligand hepatocyte growth factor [HGF]), MET mediated phosphorylation of downstream signalling proteins, as well as proliferation and survival of MET dependent cancer cells.

It has been developed as a targeted therapy for solid tumours, including locally advanced or metastatic NSCLC with MET dysregulations (MET mutation and/or MET amplification). This application proposes an initial indication in advanced / metastatic NSCLC with exon 14 skipping mutations (hereafter referred to as NSCLC with METex14).

The CHMP adopted a positive opinion for the following indication:

Tabrecta as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum based chemotherapy.

Treatment with Tabrecta should be initiated by a physician experienced in the use of anticancer therapies.

Patients have to be selected for treatment with Tabrecta based on the presence of genetic alterations leading to a METex14 skipping mutation in tumour tissue or plasma specimens using a validated test. If a genetic alteration is not detected in a plasma specimen, tumour tissue should be tested (see sections 4.4 and 5.1).

The recommended dose of Tabrecta is 400 mg orally twice daily with or without food.

Treatment should be continued based on individual safety and tolerability and as long as the patient is deriving clinical benefit from therapy.

If a dose of Tabrecta is missed or vomiting occurs, the patient should not make up for the dose, but take the next dose at the scheduled time.

Dose modifications

The recommended dose reduction schedule for the management of adverse reactions based on individual safety and tolerability is listed in Table 1.

Table 1: Tabrecta dose reduction schedule

Dose level	**Dose and schedule**	**Number and strength of tablets**
Starting dose	400 mg twice daily	Two 200 mg tablets / twice daily
First dose reduction	300 mg twice daily	Two 150 mg tablets / twice daily
Second dose reduction	200 mg twice daily	One 200 mg tablet / twice daily

Doses of Tabrecta below 200 mg twice daily have not been investigated in clinical studies.

Recommendations for dose modifications of Tabrecta for adverse reactions are provided in Table 2.

Table 2: **Tabrecta dose modifications for the management of adverse reactions**

Adverse reaction	**Severity**	**Dose modification**
Interstitial lung disease (ILD)/pneumonitis	Any grade treatment-related	Permanently discontinue Tabrecta.
Isolated ALT and/or AST elevations from baseline, without concurrent total bilirubin increase	Grade 3 (>5.0 to ≤20.0 x ULN)	Temporarily withhold Tabrecta until recovery to baseline ALT/AST grade. If recovered to baseline within 7 days, then resume Tabrecta at the same dose, otherwise resume Tabrecta at a reduced dose as per Table 1.
	Grade 4 (>20.0 x ULN)	Permanently discontinue Tabrecta.
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or haemolysis	If patient develops ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN, irrespective of baseline grade	Permanently discontinue Tabrecta.

Isolated total bilirubin elevation from baseline, without concurrent ALT and/or AST increase	Grade 2 (>1.5 to ≤3.0 x ULN)	Temporarily withhold Tabrecta until recovery to baseline bilirubin grade. If recovered to baseline within 7 days, then resume Tabrecta at the same dose, otherwise resume Tabrecta at a reduced dose as per Table 1.
	Grade 3 (>3.0 to ≤10.0 x ULN)	Temporarily withhold Tabrecta until recovery to baseline bilirubin grade. If recovered to baseline within 7 days, then resume Tabrecta at a reduced dose as per Table 1, otherwise permanently discontinue Tabrecta.
	Grade 4 (>10.0 x ULN)	Permanently discontinue Tabrecta.
Serum creatinine increased	Grade 2 (>1.5 to ≤3.0 x ULN)	Temporarily withhold Tabrecta until recovery to baseline serum creatinine grade. If recovered to baseline, then resume Tabrecta at the same dose level.
	Grade 3 (>3.0 to ≤6.0 x ULN)	Temporarily withhold Tabrecta until recovery to baseline serum creatinine grade. If recovered to baseline, then resume Tabrecta at a reduced dose as per Table 1.
	Grade 4 (>6.0 x ULN)	Permanently discontinue Tabrecta.
Vomiting	Grade 2	Temporarily withhold Tabrecta until resolved to grade ≤1. If resolved to grade ≤1 then resume Tabrecta the same dose level.
	Grade 3	Temporarily withhold Tabrecta until resolved to grade ≤2. If resolved to grade ≤2 then resume Tabrecta at a reduced dose as per Table 1.
	Grade 4	Temporarily withhold Tabrecta until resolved to grade ≤2. If resolved to grade ≤2 then resume Tabrecta at a reduced dose as per Table 1.
Other adverse reactions	Grade 2	Maintain dose level. If intolerable, consider temporarily withholding Tabrecta until resolved, then resume Tabrecta at a reduced dose as per Table 1.
	Grade 3	Temporarily withhold Tabrecta until resolved, then resume Tabrecta at a reduced dose as per Table 1.
	Grade 4	Permanently discontinue Tabrecta.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal. Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events). Baseline = at the time of treatment initiation.		

2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not

considered to be of major public health interest. This was based on

- the number of limitations associated to data coming from a small exploratory uncontrolled study
- the uncertainty regarding prognostic/predictive relevance of METex14 skipping mutations.

With this in mind, it was unclear whether capmatinib treatment would address an unmet need in the proposed broad indication of NSCLC patients with a METex14 skipping mutation, especially in the first-line setting.

Novartis received scientific advice concerning capmatinib drug substance manufacturing process from the Scientific Advice Working Party (SAWP) in Oct-2014, adopted by the Committee for Medicinal Products for Human Use (CHMP) on 18-Dec-2014 and implemented in the quality module of this marketing authorization application.

Once data was available from Study A2201 DCO 15-Apr-2019, Novartis again sought advice from the CHMP SA (written advice was provided on 17-Oct-2019) regarding the clinical development and intended regulatory submission for capmatinib, which included a proposal for the inclusion of a real-world evidence (RWE) study to serve as an external control arm.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 150 mg or 200 mg of capmatinib as active substance. The product contains the dihydrochloride salt in monohydrate form.

Other ingredients are:

Tablet core: cellulose microcrystalline, mannitol, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, sodium laurilsulfate

Film-coating (150mg): hypromellose, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172)

Film-coating (200mg): hypromellose, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172)

The product is available in PCTFE/PVC (polychlorotrifluoroethylene/polyvinyl chloride) blisters backed with an aluminium lidding foil as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of capmatinib dihydrochloride is 2-Fluoro-*N*-methyl-4-[7-(quinolin-6-ylmethyl) imidazo[1,2-*b*][1,2,4]triazin-2-yl]benzamide—hydrogen chloride—water (1/2/1) corresponding to the molecular formula $C_{23}H_{17}FN_6O \cdot 2HCl \cdot H_2O$. It has a relative molecular mass of 412.43 g/mol (free base) or 503.36 g/mol (salt form on monohydrate basis) and the following structure:

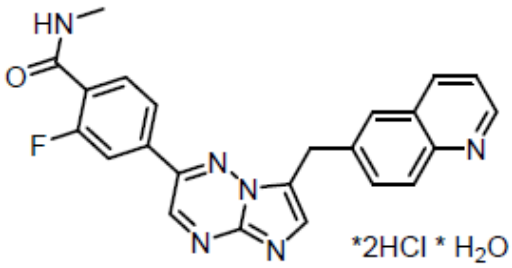


Figure 1: active substance structure

The chemical structure of capmatinib dihydrochloride was elucidated by a combination of elemental analysis, high resolution mass spectrometry, ^{1}H and ^{13}C-NMR spectroscopy, infrared spectroscopy and UV-Vis spectroscopy. The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD), X-ray crystallography, differential scanning calorimetry and thermogravimetric analysis.

The active substance is a yellow, slightly hygroscopic powder with a pH-dependent solubility which increases at low pH. Capmatinib dihydrochloride has a non – chiral molecular structure and shows polymorphism, which is adequately controlled by the proposed manufacturing process.

2.4.2.2. Manufacture, characterisation and process controls

Capmatinib dihydrochloride is manufactured by a convergent approach, with two steps in the side chain, six steps in the main chain and one sieving step.

The selection of starting materials for the synthesis of capmatinib dihydrochloride is in line with the general principles outlined in the ICH Q11 guideline on Development and Manufacture of Drug Substances. The starting materials are clearly identified, and their selection justified, the proposed manufacturers are declared, their routes of synthesis described, and the proposed specifications (tests, limits and analytical procedures) are stated and justified. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. An assessment of potential genotoxic impurities has been performed in conformance with ICH M7.

A risk assessment of potential sources of elemental impurities in the active substance was carried out in line with ICH Q3D.

The active substance is packed in a polyethylene (PE) bag or in a PE bag from continuous PE liner. The bag is placed into an additional PE bag and stored in a metal drum. The packaging material complies with Ph. Eur. 3.1.3 Polyolefins monograph and with the EC directive 2002/72/EC and EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification includes tests for appearance, particle size (laser light diffraction), identity (IR, XRPD), residual solvents (GC), water content (KF), Sulphated Ash (Ph. Eur.), Metals by ICP-MS, clarity of solution (Ph. Eur.), assay of salt forming agent (titration), impurities (HPLC), assay (HPLC) and microbial quality (TAMC, TYMC, *E.coli*) (Ph. Eur.).

Parameters included in the specification cover all the critical aspects for ensuring the quality of the active substance.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The specification includes particle size control. Residual solvents requirements have been set in accordance with ICH Q3C and based on data generated on development and commercial scale batches.

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.

Comprehensive batch analysis data from development, pilot and commercial scale batches of the active substance are provided. Differences between early development and commercial scale batches are presented and justified. The provided batch results confirm that the manufacturing process consistently yields active substance of the required quality.

2.4.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package under intermediate, long term and accelerated conditions according to the ICH guidelines were provided. The following parameters were tested: appearance, clarity of solution, identity by XRPD, water content, specified impurities, unspecified impurities, total impurities, assay and microbial quality. The analytical methods used were the same as for release and were stability indicating.

All results generated to date from the long term, intermediate and accelerated storage conditions are well within the specification limits for all quality characteristics. Photostability testing following the ICH guideline Q1B was performed on one pilot scale batch. Based on the results it is concluded that capmatinib dihydrochloride is light sensitive and should be protected from light.

Results from stress testing under thermal, oxidative and hydrolytic conditions were also provided. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed re-test period and storage conditions.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Tabrecta 150 mg is presented as pale orange brown, ovaloid, curved film-coated tablets with bevelled edges, unscored, debossed with ‘’DU’’ on one side and “NVR” on the other side with a size (length x width) of approximately 18.3 mm x 7.3 mm.

Tabrecta 200 mg is presented as yellow, ovaloid, curved film-coated tablets with bevelled edges, unscored, debossed with ‘’LO’’ on one side and “NVR” on the other side with a size (length x width) of approximately 20.3 mm x 8.1 mm.

The different dosage strengths differ only in the tablet size, the type of debossment and the colour of the film-coat.

The pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) was defined as an immediate release dosage form for oral administration with

commercial dose planned between 200 to 400 mg twice daily, that meets compendial and other relevant quality standards.

Several manufacturing process technologies were explored based on active substance properties and dosage regimen to achieve a suitable and robust manufacturing process that consistently meets finished product CQAs.

The formulation and manufacturing process development have been evaluated through the use of risk assessment and design of experiments (DoE) to identify the critical product quality attributes (CQAs) and critical process parameters (CPPs). A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes.

The CQAs and CPPs have been adequately identified. The physicochemical characteristics of the active substance that could influence the performance of the finished product and its manufacturability were identified and discussed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for the iron oxide black, iron oxide red and iron oxide yellow which comply with the EU food additives regulation. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

A compatibility study with standard solid oral excipients was performed using different mixtures of capmatinib dihydrochloride active substance and excipients stored at long-term conditions and stress conditions in open and closed containers.

All relevant functionality-related characteristics (FRCs) have been sufficiently discussed for each excipient.

In line with the QTPP, capmatinib dihydrochloride has been formulated as an immediate release solid oral dosage form.

The pivotal clinical study was initiated with capmatinib 100 mg and 200 mg film-coated tablets. The 150 mg dosage strength was added later in the development to replace the 100 mg tablets. The similarity of the 150 mg film-coated tablet with the 100 mg and 200 mg film-coated tablets was adequately demonstrated by *in vitro* and *in vivo* studies.

In order to develop a suitable dissolution method, the pH has been evaluated along the physiological range. Results of in vitro dissolution tests at three different buffers (pH 1, 4.5 and 6.8) and the media intended for finished product release, have been reported. Basket apparatus is used, and the stirring speed is justified and acceptable. The discriminatory power of the method and the proposed specification has been sufficiently demonstrated. The primary packaging is PCTFE/PVC (polychlorotrifluoroethylene/polyvinyl chloride) blisters backed with an aluminium lidding foil. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of following steps: wet granulation, milling, drying, blending, compression and film coating, The manufacturing process has been adequately described. The process is considered to be a standard manufacturing process.

The suitability of the proposed bulk product container closure system for storage and transport is justified and the material is described along with its control specification. The product shelf-life is calculated according to the "Note for Guidance on the start of shelf-life of the finished dosage form".

Process validation data are presented on three consecutive production scale batches per strength. It has been demonstrated 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 and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), identity (HPLC, NIRS, UV), degradation products (HPLC), water content (KF), assay (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (content uniformity by HPLC or NIRS) and microbiological quality (TAMC, TYMC, *E. coli*) (Ph. Eur.).

The parameters included in the finished product specification cover all the critical aspects for ensuring the quality, safety and efficacy of the product.

The limits for related substances at both release and shelf-life are in accordance with ICH Q3B and are considered acceptable. All other limits have also been satisfactorily justified.

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

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed 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, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results are provided for representative number of batches (clinical, registration, pre-validation), including three validation production scale batches of 150 and 200 mg, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability studies are completed for three batches each of capmatinib 100 mg and 200 mg film coated tablets as well as for six batches of capmatinib 150 mg film-coated tablets in PCTFE/PVC blisters according to ICH stability conditions. All batches were produced using the same equipment type and manufacturing process as intended for commercial manufacturing. The batches of Tabrecta are

representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, dissolution, water content, assay, degradation products and microbial quality. Additional tests were tested for information. The analytical procedures used are stability indicating.

The results of all tested quality attributes on samples stored under long term and accelerated conditions remained within the specification limits. The observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

Photostability testing was performed on one pilot batch of 100 mg, one pilot and one production batch of 150 mg and one production batch of 200 mg dosage strength in line with ICH Q1B "Photo stability Testing of New Drug Substances and Products". Tablets are found to be chemically stable when exposed to light.

Tabrecta film-coated tablets are sensitive to moisture absorption as evidenced by observed physical changes in water content, tablet thickness and crushing strength when stored at elevated humidity.

Based on available stability data, the proposed shelf-life of 36 months without any special temperature storage condition as stated in the SmPC (section 6.3) is acceptable. The product should be stored in the original package in order to protect from moisture.

2.4.3.5. Adventitious agents

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

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

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

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

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Capmatinib (INC280, INCB28060) is presented as an adenosine triphosphate (ATP) competitive, reversible low molecular weight inhibitor of the MET receptor tyrosine kinase (RTK). The proto-oncogene MET encodes the high-affinity receptor for hepatocyte growth factor (HGF), which is the only known ligand for this receptor. Binding of HGF to MET causes receptor multimerization, phosphorylation, and activation. MET alterations (including activating mutations, overexpression, gene amplification, and translocations) can lead to autophosphorylation of tyrosine residues and downstream activation of specific pathways, which promote cell proliferation, survival, migration and angiogenesis.

Several mechanisms have been identified by which the MET pathway becomes aberrantly activated in cancer. Among these, a set of MET mutations that cause skipping of exon 14 is of particular importance in lung cancer. Another mechanism of MET dysregulation in cancer is high-level MET gene amplification, leading to constitutive ligand-independent kinase activation. Chromosomal translocations leading to MET fusion proteins have also been reported in lung cancer and were associated with clinical response to MET inhibition. Finally, MET amplification can cause resistance to EGFR inhibitors and may account for approximately 20% of relapse cases in non-small cell lung cancer subjects receiving EGFR-targeted therapy.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro and in vivo primary pharmacodynamic studies were performed to investigate antitumour activity of capmatinib in cell lines and tumour models in which MET was activated by several mechanisms. Both biochemical and cellular assays have been performed in the in vitro characterization, and xenograft animal models for the in vivo investigation.

Primary pharmacodynamics *in vitro*

The in vitro characterization of capmatinib was done in enzymatic and cell-based models.

The enzymatic assays showed the activity of INC280 against wild-type MET kinase at an inhibitory concentration of nM. Not only wild type enzyme, but also mutants were tested, and it was observed that some mutations reduced the activity of capmatinib (Table 3).

Table 3. In vitro activity of capmatinib against human WT and mutant MET enzymes

Enzyme	IC_{50} (nM)	N
Wild type MET	0.13 ± 0.05	17
Mutant H1094Y	0.3	2
Mutant L1195V	736	2
Mutant Y1230C	1077	2
Mutant Y1235D	14	2

It is noted that some of these mutants (Y1230C and L1195V) have been shown to be involved in both on-target (MET mutations) and off-target (bypass signalling) resistance mechanisms to MET inhibitors, including capmatinib (Tiedt et al 2011, Baltschukat et al 2019, Fujino et al 2019, Dagogo-Jack et al 2021, Recondo et al 2020).

Only 4 cell lines were used with contained exon 14 skipping mutations. One of these, the NCI-H596 lung cancer cell line, showed no activity of capmatinib on cell proliferation, although in another experiment with this cell line treatment did inhibit phosphorylation of the receptor. The other cell lines showed no loss of activity of capmatinib due to the presence of these mutations, but these cells are mouse fibroblasts instead of cancer cells. Although binding of capmatinib to mutated MET has not been thoroughly investigated in preclinical experimental systems, clinical data could provide a justification for the absence of these studies.

Further studies revealed the selectivity of capmatinib for MET kinase (report T07-07-08, RD-2017-00516 and RD-2018-00093). In these 57- and 442-kinases panel, it was concluded the preference of INC280 for MET kinase, including mutants M1250T and Y1235D. Other kinases in which capmatinib showed potential binding were ABL-1, AXL, CDK11, IRAK1, PIP5K2C, and YSK4, although binding constant values indicated high selectivity for MET kinase (lower K_d value)

Cellular assays involved MET-phosphorylation, cell proliferation, colony formation, migration/wound healing or apoptosis/DNA fragmentation. Activity was inhibited by capmatinib (including cell lines with a MET exon 14 skipping mutation), except those that lack MET-dysregulation features.

The biochemical characterization of the three main metabolites of capmatinib (M8, M16, and M18) was studied in a highly MET-amplified and MET-dependent gastric cell line (report RD-2014-00427). Results revealed that M16 was inactive, and both M8 and M18 presented less activity than the parental compound (52x and 2.5x, respectively). The contribution of these metabolites was negligible, given the low systemic exposure showed (13% and 7%, respectively).

Primary pharmacodynamics *in vivo*

The *in vivo* activity was investigated in PDX models (highest MET mRNA expression). These studies showed that capmatinib inhibited tumour growth independently of the MET-gene copy number, although only one carried a MET exon 14 skipping mutation (five-day treatment with a moderate reduction of volume reduction). Furthermore, capmatinib was also able to produce a regression in a different PDX collection bearing this mutation in the absence of MET amplification (LU5381). No data were shown in an *in vivo* model harbouring MET exon 14 skipping alterations and a concomitant MET amplification.

Other *in vivo* models were reported via bibliographic references, which included a study with high levels of MET and its ligand HGF (S114) (Liu *et al.*, 2011); and a MET-amplified gastric cancer cell line GTL-16luc2 (RD-2010-000650).

PK/PD analysis was presented from the pharmacology studies, in order to determine an inhibitory concentration in efficacy assays. In mice subcutaneously injected with mouse fibroblasts transfected with human MET and the ligand HGF (S114 cell line), the IC_{50} estimated was 19.6nM, which considering PPB in humans resulted in an IC_{50} value of 22nM. The IC_{90} and IC_{95} were 108nM and 320nM, respectively.

A patient-derived xenograft (PDX) model was implanted intracranially in nude mice containing a NSCLC-AC with MET exon 14 skipping mutation acquired from a non-smoking patient. Tumour-bearing mice were treated orally for 14 consecutive days with capmatinib at 10 mg/kg (group B), capmatinib at 2.5 mg/kg (group C) or vehicle as a control arm (group A), and tumour volume was monitored twice weekly by Magnetic Resonance (MR) imaging. Results showed that capmatinib treatment led to a significant lower tumour volume compared to the control group (report RD-2021-00352).

2.5.2.2. Secondary pharmacodynamic studies

Potential off-target activity of capmatinib and its metabolite M16 has been analysed in receptor binding and screening assays.

In the case of parental drug, it was tested in a 154-unique target panel (report RD-2016-00046), in which activity (<10μM) was reported in rat VMAT2 monoamine transporter uptake assay (IC_{50} = 2.0μM), the angiotensin receptor AT1 binding assay (IC_{50} = 4.4μM), the phosphodiesterases PDE3 (IC_{50} = 4.7μM,) and PDE4 (IC_{50} = 5.1μM) and the acetylcholinesterase assay (IC_{50} = 5.7μM). Taking into account the estimated human therapeutic plasma free drug C_{max} (0.464μM) and brain penetration (10%), it was considered that INC280 at therapeutic doses is not expected to have effects on these targets.

In the screening of the metabolite M16 (CMN288), it had no effect on hERG (report RD-2016-00063). Activity was observed on the dopamine transporter (96%, IC_{50} = 0.25μM), bile salt export pump (BSEP, 70%; IC_{50} = 1.5μM), benzodiazepine receptor (66%, IC_{50} = 5.7μM), phosphodiesterase PDE3A (65%, IC_{50} = 4.6μM), vesicular monoamine transporter (VMAT2, 65%, IC_{50} = 6.8μM), phosphodiesterase PDE4D (40%, IC_{50} = 10μM) and acetylcholinesterase (44%, IC_{50} = 14μM). The mean free Cmax for CMN288 at steady state was of 0.013μM (INC280 at 400 mg bid), and extrapolated free-drug Cmax in the brain at the range of 0.0013 to 0.013μM (assuming 10% to 100% brain penetration based on whether efflux transporter is involved in CMN288 distribution into the brain), concluding no relevant off-target effects under therapeutic conditions.

2.5.2.3. Safety pharmacology programme

In vitro

Safety pharmacology in vitro assays addressing the cardiovascular system (study T08-02-06) showed that capmatinib inhibited hERG current by 13.7%, 36.7% and 60.6% at 3, 10 and 30μM, respectively with estimated IC_{50}=18.7μM (40x expected free drug Cmax (0.464 μM) at the recommended dose of 400 mg twice daily in humans).

In vivo

No cardiovascular effects (haemodynamic or electrocardiographic) were reported in monkeys treated at 150 mg/Kg with capmatinib (study 1070420).

No effects were reported in rats treated at 120 mg/Kg with capmatinib on the respiratory and CNS (study 1070421).

2.5.2.4. Pharmacodynamic drug interactions

No dedicated pharmacodynamic drug interactions studies were conducted.

2.5.3. Pharmacokinetics

Methods of analysis

Bioanalytical methods were validated for quantification of capmatinib plasma of mouse (DMPK R1100266F), rat (INCYTE-DMB-08.119.1 and DMPK R1100266C), rabbit (DMPK R1100266D), dog (DMPK R1300899) and monkey (INCYTE-DMB-08.120.1 and DMPK R1100266).

The toxicokinetic analysis of the pivotal studies were conducted in compliance with GLP (studies DMPK-INCYTE-DMB-08-102, DMPK-INCYTE-DMB-08-103, PCS-RT10-02-02, and PCS-R1070417).

Samples from the pivotal studies were analysed by validated LC-MS/MS.

Absorption

Absorption parameters were described after administration (po or iv) with capmatinib. After oral dosing, time to maximum concentration was 0.3-7.0 hours in nonclinical species and absorption value 51.1%. Bioavailability values indicated a great variability after oral dose (24-100%). The systemic plasma clearance was low-to-moderate in all species, except in dogs that was higher (lower PPB). A gender effect was observed in mice and rats (not in dogs and monkeys) in terms toxicokinetics, which was attributed to a gender-dependent expression of CYP enzymes and AO in these species (Martignoni *et al.,* 2006). Elimination half-life was ranged between 0.7-4.3 hours in mouse, rat, dog and monkey. After intravenous administration blood clearance was low-to-moderate and the volume of distribution was low-to-medium.

One metabolite was identified to have an exposure greater than 10% (M16).

Distribution

PPB values and B/P concentration ratios were determined in nonclinical species, indicating similar values to humans in all cases except for dogs (lower PPB value as well as higher B/P value).

Tissue distribution studies indicated the highest levels of radiolabelled capmatinib in melanin-containing tissues such as in eye (choroid) and eye (ciliary body), followed by hair (follicle), hair (tactile), meninges and preputial gland. Radioactivity in these tissues was detectable at 168 hours postdose. After repeat dosing, exposure was higher than after single dose.

Capmatinib crossed the blood brain barrier in rats with a brain to blood exposure (AUCinf) ratio of approximately 9%.

Metabolism

Metabolism of capmatinib was investigated both *in vitro* (hepatocytes of mouse, rat, dog, monkey and human and in liver microsomes of human) and *in vivo* (rat, monkey and human). Biotransformation investigations showed a major role for phase I metabolic reactions (oxygenation, N-dealkylation, carboxylic acid formation and hydrogenation), and phase II reactions also involved (glucuronidation). Correspondent metabolites were identified. In plasma, capmatinib was the major component, followed by metabolite M16 (>10%) in rat, monkey and human. M8 was also identified with a minor contribution.

Excretion

Elimination of capmatinib was investigated in rat, monkey and human. The major route of elimination was metabolism followed by excretion in bile and a minor secretion into faeces. Excretion in urine was negligible.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

The applicant established the NOAEL values after single dose of capmatinib in mouse and monkey at 600 mg/Kg (Study T07-11-12 and Study T07-11-13). In rat, the LD_{50} cut-off value was considered to be 200 mg/kg (Study 503089).

2.5.4.2. Repeat dose toxicity

In terms of toxicological characterization, capmatinib has been evaluated non-clinically according to ICH M3 and S9 guidelines (single dose and repeated dose toxicity, genotoxicity studies, reproductive toxicology, and phototoxicity). All pivotal studies were conducted in accordance with GLP. The oral route was chosen because it is the intended route of administration in humans. The rat and monkey were selected as the rodent and non-rodent species, respectively, for repeat-dose toxicity testing because both have historically been used in safety evaluations, and both species have a highly conserved MET receptor target protein sequence. Both species also displayed all of the major metabolic pathways observed in humans.

Pivotal repeat dose toxicity studies were conducted in rats and monkeys for a 4- and 13-week dosing period. Both rats and monkeys are considered pharmacologically and metabolically relevant species. The applicant established the NOAEL values (40 mg/kg/day for males and 20 mg/kg/day for females in the case of rat, and 30 mg/Kg/day for monkey species), based on the findings observed in the 13-week studies (study T10-02-02 and study 1070417).

Study T08-04-11: 4-week oral toxicity in Sprague Dawley rats

Animals were orally dosed with capmatinib (0, 20, 60 and 120 mg/kg/day for males and 0, 10, 30 and 60 mg/kg/day for females) for 4 weeks, followed by a 4-week recovery period.

Mortality was reported in the high dose group in both males and females. Toxicity was also noted in all dose levels tested: Serum chemistry alterations were noted in all dose groups; microscopic brain (white matter vacuolation; 120 mg/kg/day males and 60 mg/kg/day females) and pancreas findings (cytoplasmic vacuolation of pancreatic acinar cells; 60 and 120 mg/kg/day group males and 30 and 60 mg/kg/day group females) were also noted. Finally, clinical signs of unkempt appearance, dermal atonia, tremors and/or convulsions, lower body weights and food consumption and hematology alterations were observed in the high dose (120 mg/kg/day group males and 60 mg/kg/day group females).

Partial to full recovery was observed in the low and mid-dose groups in all parameters with the following exception: total bilirubin levels remained increased, but without a clear dose response, in the 20 and 60 mg/kg/day group males following the 28-day recovery period.

A NOEL for this study was undetermined. Based on the low level of incidence and severity, and the reversibility of pancreatic changes identified in males and females at their respective mid-doses, the applicant established the NOAEL value to be 60 mg/kg/day in males and 30 mg/kg/day in females (Table 4).

Table 4. Summary of capmatinib on day 27 in rats (study T08-04-11)

Time	Dose (mg/kg) (M/F)	Males		Females	
		Cmax	$AUC_{(0-24h)}$	Cmax	$AUC_{(0-24h)}$
Day 27	20 / 10	6.26	40.2	10.1	37.6
	60 / 30	19.1	143	22.6	145
	120 / 60	27.2	272	20.7	214

Cmax (µM); AUC(0-24hr) (µM*h)

Study T10-02-02: A 3-month oral toxicity and toxicokinetic study in Sprague Dawley Rats

Capmatinib (0, 20, 40, 60, and 90 mg/kg/day for males and 0, 10, 20, 30, and 45 mg/kg/day for females) was orally administered to rats for 90 days, followed by an additional 13-week recovery period.

Mortality was observed in animals of the high dose group.

Capmatinib was not tolerated in males at ≥ 60 mg/kg/day and females at ≥ 30 mg/kg/day as mortality, and clinical observations were noted in all groups (unkempt appearance and clear material on various body surfaces correlated with an increased incidence of salivation noted during FOB evaluation). Also, clinical pathology alterations were noted: haematology alterations (included a reversible, non-adverse, modest lymphocytosis in males at dosage levels ≥ 40 mg/kg/day and in the 30 mg/kg/day group females; and additionally, the monocyte and large unstained cell counts were higher in the 60 mg/kg/day group males); serum chemistry alterations (included lower potassium concentrations in the 60 and 90 mg/kg/day males and the 20 and 30 mg/kg/day females; and a higher amylase concentration was noted in the 60 mg/kg/day group males.

For the early death animals, the 2 males from the 90 mg/kg/day toxicology group observed with tremors or convulsions were noted with microscopic changes in the brain (white matter vacuolation of the caudate/putamen region). Other microscopic changes were evident in the pancreas (minimal pancreatic acinar cell vacuolation) of the 90 mg/kg/day group males, with a lower incidence being noted in the 45 mg/kg/day group females.

At the primary necropsies, degeneration and white matter vacuolation of the thalamus in the brain were evident in 1 male and white matter vacuolation of the caudate/putamen region was evident in 2 additional males from the 60 mg/kg/day group. Pancreatic acinar cell apoptosis also was evident at study week 13 in the 60 mg/kg/day group males, correlating with the higher amylase concentration. The magnitude of pancreatic change noted in this study was not considered adverse. No remarkable findings were noted at the recovery necropsies.

The NOEL was not determined and the NOAEL was 40 mg/kg/day for males and 20 mg/kg/day for females. Plasma levels of the study are shown in Table 5.

Table 5. Summary of capmatinib toxicokinetics on day 90 in rats (study T10-02-02)

Time	Dose (mg/kg) (M/F)	Males		Females	
		Cmax	$AUC_{(0\text{-}24h)}$	Cmax	$AUC_{(0\text{-}24h)}$
Day 90	20 / 10	10.5	58.1	7.44	42.4
	40 / 20	23.5	118	17.1	94.4
	60 / 30	28.4	254	24.3	155
Day 28/56	90 / 45	34.6[a]	222[a]	33.5[a]	182[a]

Cmax (µM); AUC(0-24hr) (µM*h)

Study T08-01-08: A 4-week oral toxicity study with Cynomolgus monkeys

Cynomolgus monkeys were doses by oral gavage with capmatinib (0, 30, 75, and 150 mg/kg/day) for 4 weeks with a 4-week recovery period. Although no treatment related mortality occurred in the study, one female at 150 mg/kg/day was found dead on day 35 (seventh day of the recovery phase). The applicant considered that based on the gross and microscopic findings, the cause of death was bacterial sepsis, and the clinical pathology changes on day 27 were likely to be due to the animal's condition.

Discolored urine and/or abnormal feces color were noticed in all test article-treated groups. Those observations were considered possibly test article-related due to intense yellow color of the test article. There were no additional test article-related clinical signs, and no test article-related changes in body weight, electrocardiographic or physical examination parameters, ophthalmic changes, changes in hematology, coagulation, or urinalysis parameters, or necropsy findings.

Test article-related serum chemistry findings were limited to reversible, decreased serum cholesterol levels at 150 mg/kg/day; reversible, minimally decreased serum calcium values at ≥ 75 mg/kg/day; and generally reversible, minimally higher serum amylase values at 150 mg/kg/day. While possibly test article-related, these changes were not considered adverse.

Test article-related findings were reported in the kidney and pancreas. Pancreatic acinar cell apoptosis was increased in incidence and severity in monkeys at 75 and 150 mg/kg/day. In the 30 mg/kg/day monkeys, the incidence of acinar cell apoptosis was slightly increased compared to controls; however, the severity was uniformly increased, suggesting a test article-related effect. Based on the relatively low level of histologic change, the lack of clinical correlate, the pancreatic finding at 30 mg/kg was considered non-adverse by the applicant. Findings described in the kidney in monkeys at 75 and 150 mg/kg consisted of deposits of amphophilic material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen. Following a 28-day recovery period, histological findings were limited to mild, renal interstitial and tubular, amphophilic deposits with multinucleated giant cells, in a single high-dose group (150 mg/kg/day) animal. Pancreatic acinar cell apoptosis was not observed in the recovery group animals, indicating resolution of this finding following cessation of dosing. The applicant considered the NOAEL for this study was 30 mg/kg/day (TK values are shown in Table 6).

Table 6. Summary of capmatinib toxicokinetics on Day 27 in monkeys (study T08-01-08)

Time	Dose (mg/kg) (M/F)	Males		Females	
		Cmax	$AUC_{(0\text{-}24h)}$	Cmax	$AUC_{(0\text{-}24h)}$
Day 27	30	34.8	96.7	34.1	111
	75	52.7	220	56.6	263
	150	51.8	350	49.7	334

Cmax (µM); AUC(0-24hr) (µM*h).

Study 1070417: A 13-week oral toxicity study in the monkey

Cynomolgus monkeys were administered with capmatinib (0, 10, 30 and 75 mg/kg/day) by oral gavage for 13 weeks, followed by an 8-week recovery period.

There were neither mortality nor treatment related effects on body weight, food consumption, ophthalmology, electrocardiograph, hematology coagulation parameters, organ weights and macroscopic observations at any dose levels. Occasional salivations were noted in the high dose animals.

Reversible minimal decreases in albumin (to 0.71X predose) and total protein as well as reversible moderate increases in amylase (up to 1.8X predose) and lipase (up to 13.2X predose) in a low number of individual animals at 75 mg/kg/day. There were no microscopic observations correlating to these clinical chemistry changes. In the liver of males at 75 mg/kg/day, there was reversible minimal to mild subcapsular neutrophilic infiltration associated with single cell necrosis.

In conclusion, based on the histopathology findings in the liver, and the uncertain toxicological significance of changes seen in amylase and lipase at the dose of 75 mg/kg/day, the applicant established the NOAEL value at 30 mg/kg/day (TK in Table 7).

Table 7: Summary of capmatinib toxicokinetics on Day 87 in monkeys (study 1070417)

Time	Dose (mg/kg) (M/F)	Males		Females	
		Cmax	$AUC_{(0\text{-}24h)}$	Cmax	$AUC_{(0\text{-}24h)}$
Day 87	10	1560	7100	2210	7310
	30	7200	42300	5430	23400
	75	18600	119000	15100	79300

Cmax (ng/mL); AUC(0-24hr) (ng*hr/mL).

2.5.4.3. Genotoxicity

The potential genotoxicity of capmatinib has been investigated in the standard test battery (GLP compliant): one *in vitro* bacterial assay (Ames test, study 1070233), one *in vitro* test in cultured human peripheral blood lymphocytes (chromosome aberration, study 1070418), and one *in vivo* test (micronucleus, study 1170161).

Capmatinib resulted negative in the genotoxicity test battery. The results are shown in Table 8.

Table 8. Results of the genotoxicity tests conducted with capmatinib

Table 17.

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria	Salmonella typhimurium TA98, TA100, TA1535, TA97a, and TA102	Maximum conc. 5000μg/plate (+/- S9)	Negative
In vitro chromosome aberration assay	HPBL	3+17h: -S9 (50-400μg/mL) 3+17h: +S9 (50-400μg/mL) 20h: -S9 (5-400μg/mL) 3+17h: +S9 (10-300μg/mL)	Negative
Chromosomal aberrations in vivo	Rat, micronuclei in bone marrow	0, 50, 100, and 200 mg/Kg/day (male) 0, 17.5, 35, and 70 mg/Kg/day (female)	Negative

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted.

2.5.4.5. Reproductive and developmental toxicity

Neither fertility and early embryonic development nor pre- and postnatal toxicology studies have been conducted with capmatinib. There were no findings in reproductive organs in repeated dose toxicity studies in rats and monkeys. However, prostate was reported to be affected in a 4-week toxicity study for impurity qualification (no dose response observed).

In embryo-foetal development studies in rats and rabbits, capmatinib was teratogenic and foetotoxic at dose levels not eliciting maternal toxicity. In rats (Study 11701600), decreased foetal weight and increased incidence of litters and foetuses with limb malformations were observed at the maternal exposure of ≥0.89 exposure multiples of the anticipated clinical exposure (based on the AUC). In rabbits, limb, lung and tongue malformations were seen at the maternal exposure of ≥0.025 exposure multiples of the anticipated clinical exposure (study 1170159).

No toxicity studies in juvenile animals were conducted as it is not intended to be used in paediatric patients (specific waiver from EMA-PDCO).

2.5.4.6. Toxicokinetic data

AUC ratio were within the same range when compared exposure in humans and NOAEL values established by the company in the nonclinical species (rat and dog). In the case of female monkeys, ratio value was below 1 (Table 9).

Table 9. Animal exposure multiples of a 400 mg twice daily dose in humans

Animals					Exposure multiples [a]	
Species	NOAEL (mg/kg/day)	Sex	AUC0-24h (µM •h)	Cmax (µM)	Based on a mean AUC0-24h.ss[d]	Based on mean Cmax[d]
Rat [b]	30	F	145	22.6	1.5	1.9
	60	M	143	19.1	1.5	1.6
Rat [c]	20	F	94.4	17.1	1.0	1.5
	40	M	118	23.5	1.2	2.0
Monkey [b]	30	F	111	34.1	1.1	2.9
	30	M	96.7	34.8	1.0	3.0
Monkey [c]	30	F	56.7	13.2	0.6	1.1
	30	M	102.6	17.5	1.0	1.5

[a] Calculation based on total plasma concentration.
[b] NOAEL of 28-day toxicity studies in rats or monkey.
[c] NOAEL of 13-week toxicity study in rats and monkeys.
[d] Based on PK data of patients at 400 mg tablet BID (800 mg/day) at Cycle 1 Day 15 of [CINC280A2201].

2.5.4.7. Local Tolerance

No local tolerance studies were conducted.

2.5.4.8. Other toxicity studies

No specific immunotoxicity studies were conducted with capmatinib

As for impurities analysis, it was concluded that the presence of impurities did not change the toxicity profile of capmatinib. It is noted that findings were reported in prostate in the 4-week impurity qualification study (study 1570059), although no dose response was shown for either weight change or incidence and severity of the histopathological findings.

Phototoxicity studies revealed that capmatinib was phototoxic in vitro and the NOAEL value in vivo was 30 mg/Kg (Cmax 42400 ng/mL). In multiple dosing studies, the highest accumulation was observed in eye (lens) and adrenal (medulla) with AUClast ratios single versus multiple dosing of 41.6 and 9.01.

No evidence of ototoxicity was observed when capmatinib was administered to rats at doses of 60 and 90 mg/kg/day for up to 42 days (study 1370733).

2.5.5. Ecotoxicity/environmental risk assessment

Table 10: Summary of main study results

Substance (INN/Invented Name): capmatinib			
CAS-number (if available): 1029712-80-8			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log D_{ow}	OECD107	2.1, 2.7 and 2.7 at pH 4, 7 and 9, respectively			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log D_{ow}	2.1 to 2.7 at pH 4 to 9			Not B
Persistence	ready biodegradability	Not readily biodegradable,			
	DT50	DT50,total system at 12°C >1000 and >1000 L/kg in river and pond, respectively			vP
Toxicity	CMR	oral administration to pregnant rats and rabbits during organogenesis resulted in foetotoxicity and teratogenicity.			T
PBT-statement :	The compound is considered not as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$ (default)	0.0087	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					Foetotoxicity and teratogenicity in mammalians
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Sludge: Koc = 1839 and 12981 L/kg, Kd = 707 and 3549 L/kg, %OC = 38.47 and 27.34, respectively; Soils: Koc = 50,506, 51,811 and 344,613 L/kg, Kd = 404, 1495 and 6041 L/kg, %OC = 0.8, 3.05, 1.78, respectively			no correlation with organic carbon content (%OC)
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,whole\ system,20°C}$ = 1291 d (river), 1989 d (pond) Sediment shifting after or at 14 days = 100%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	72h-EC_{10}	435	µg/L	Growth rate
Daphnia sp. Reproduction Test/*Daphnia magna*	OECD 211	21d-EC_{10}	820	µg/L	Reproduction
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	34d-EC_{10}	410	µg/L	Growth
Activated Sludge, Respiration Inhibition Test	OECD 209	3h-NOEL	≥820	mg/ L	Not toxic to activated sludge up to and in excess of water solubility
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	Not determined		Not triggered due to low lipophilicity
Sediment dwelling organisms/ *Chironomus riparius*	OECD 218	NOEC	≥820 mg/kg (dry sediment, TOC 2.1%)		Concentration based on applied radioactivity

				2.1% o.c. Not normalised to 10% o.c. since sorption is not OC dependent

2.5.6. Discussion on non-clinical aspects

Pharmacology

The *in vitro* data showed capmatinib as a MET kinase inhibitor, with a binding activity within the range of nanomolar. Enzymatic assays showed reduced activity of capmatinib on MET mutations, involved in resistant mechanisms (on- and off-taget).

Although binding of capmatinib to mutated MET has not been thoroughly investigated in preclinical experimental systems, clinical data could provide a justification for the absence of these studies.

Only 4 cell lines were used with contained exon 14 skipping mutations. One of these, the NCI-H596 lung cancer cell line, showed no activity of capmatinib on cell proliferation, although in another experiment with this cell line treatment did inhibit phosphorylation of the receptor. The other cell lines showed no loss of activity of capmatinib due to the presence of these mutations, but these cells are mouse fibroblasts instead of cancer cells. Further, binding of capmatinib to mutated MET were not thoroughly investigated during the nonclinical development. At this point, clinical data could provide a justification for the absence of these studies. Enzymatic selectivity and cellular assays related to MET-phosphorylation, cell proliferation, colony formation, migration/wound healing or apoptosis/DNA fragmentation were conducted as part of the *in vitro* characterization.

Main metabolites (M8, M16, and M18) were characterized from a biochemical point of view, resulting in a lack of activity for M16, and less activity than the parental compound in the case of M8 and M18 (52x and 2.5x, respectively).

In vivo studies showed capmatinib inhibited tumour growth in PDX models. Only one xenograft lung cancer model with an exon 14 skipping mutation was investigated. In this model, the treatment was limited to 5 days, after which only moderate reduction of tumour volume is shown. Also, no *in vivo* preclinical study harbouring MET exon 14 skipping alterations and concomitant MET amplification was conducted, although reference to clinical data were provided. Additional *in vivo* actions were reported via bibliographic references. The applicant has described a PK/PD mouse model, in which mice were subcutaneously injected with mouse fibroblasts transfected with human MET and the ligand HGF (S114 cell line). Using this model an IC90 and IC95 were calculated for the human situation (108 and 320 nM, respectively). However, in the translation from mouse human, only protein binding was taken into account, whereas there are other factors that might influence the IC90/95 values, including but not limited to the site of the tumour, and other characteristics of the tumour cells including presence of exon 14 skipping mutations. That other factors are important in determining IC values is demonstrated by a second study, in which a gastric cancer xenograft model was used which showed much lower IC values. The IC90/95 values derived from this model are therefore of limited human relevance.

It is noted that brain metastasis is highly associated to patients with locally advanced or metastatic NSCLC with MET exon 14 skipping mutations. In this context, an efficacy study conducted in the ST3102 (MET exon 14 skipping mutation) PDX lung model, showed the reduction of tumour volume after capmatinib treatment, monitored by RMI imaging.

Potential off-target activity of capmatinib resulted in no additional actions on receptor panels.

The potential activity of capmatinib was investigated in cardiovascular, respiratory and CNS, in line with ICH S7 guidelines. *In vivo* analysis showed no effect on the analysed test systems.

No dedicated pharmacodynamic drug interactions studies were conducted, but potential interactions cannot be ruled out if capmatinib is co-administered with other inhibitors of pathways related to MET.

Pharmacokinetics

Pharmacokinetic profile of capmatinib has been adequately described in nonclinical species.

After oral dosing, time to maximum concentration was 0.3-7.0 hours and absorption 51.1%. Bioavailability indicated a great variability after oral dose (24-100%). The systemic plasma clearance was low-to-moderate in all species, except in dogs that was higher (lower PPB). A gender effect was observed in mice and rats (not in dogs and monkeys), attributed to a gender-dependent expression of CYP enzymes and AO in these species. Elimination half-life was ranged between 0.7-4.3 hours in nonclinical species. After intravenous administration blood clearance was low-to-moderate and the volume of distribution was low-to-medium.

PPB values and B/P concentration ratios indicating similar values to humans in all cases except for dogs (lower PPB value as well as higher B/P value). Tissue distribution studies indicated the highest levels of radiolabelled capmatinib in melanin-containing tissues such as in eye (choroid) and eye (ciliary body), followed by hair (follicle), hair (tactile), meninges and preputial gland. Radioactivity in these tissues was detectable at 168 hours postdose. After repeat dosing, exposure was higher than after single dose. Brain distribution analysis is described by the applicant as a minor extent, although tremors, and convulsions have been described in nonclinical studies.

Metabolism of capmatinib was investigated both *in vitro* (hepatocytes of mouse, rat, dog, monkey and human and in liver microsomes of human) and *in vivo* (rat, monkey and human). Biotransformation investigations showed a major role for phase I metabolic reactions (oxygenation, N-dealkylation, carboxylic acid formation and hydrogenation), and phase II reactions also involved (glucuronidation). One metabolite was identified to have an exposure greater than 10% (M16). In plasma, capmatinib was the major component, followed by metabolite M16 (>10%) in rat, monkey and human. M8 was also identified with a minor contribution.

The major route of elimination was metabolism followed by excretion in bile and a minor secretion into faeces. Excretion in urine was negligible.

Non-clinical information on pharmacokinetic drug interactions appears to be scarce. Most issues have nevertheless been addressed in clinical studies or PBPK simulations.

Toxicology

The applicant established the NOAEL values based on the findings observed in the 13-week study.

Target organs were adequately identified, such as pancreas (pancreatic acinar cell apoptosis and increase in amylase and lipase in both species), CNS (tremors, convulsions and histopathological findings in rats), liver (alteration of liver enzymes (both species) and subcapsular neutrophilic infiltration in monkeys) and kidney (deposits of amphophilic, crystalline-like material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen). It is noted that AUC ratio was within the same range, indicating small safety margins, when compared exposure in humans and NOAEL values established by the company in the nonclinical species (rat and dog).

CNS toxicity and histopathological changes in brain, constituted of the white matter vacuolation of the midbrain and/or thalamus, were seen in rats already at EM of ~2.9-4.4 of the anticipated clinical exposure based on AUC at the 400 mg twice daily dose (small safety margins). Transmission electron microscopic examination of the vacuoles showed myelin oedema characterized by separation of myelin sheath lamellae (myelin splitting/ballooning) with scant intraluminal debris. It is of note that rats

appear to be more sensitive to the toxicity of capmatinib than mice or monkeys, as was also evidenced in the single dose toxicity studies.

Due to severe CNS toxicity seen in rats, the applicant performed a non-GLP investigative study. In this study it was shown that capmatinib appears to downregulate the Nrg1 and Zeb2 cluster gene expression in rats; however, the mechanism by which capmatinib induces white matter vacuolation in rats is currently not clear. Finally, disturbed myelination and Nrg1 downregulation have been linked to both neurodegenerative and neuropsychiatric diseases, occurring at clinically relevant exposure levels. If these genes are involved in the mechanism of CNS toxicity is however not clear.

On the other hand, it is known that MET is expressed in neurons but also in other brain-resident cells such as oligodendrocytes, astrocytes and microglia. Its ligand HGF is recognised to induce proliferation and migration of oligodendrocyte precursor cells as well as inhibition of the proapoptotic caspase-3 pathway in oligodendrocytes. It can thus not be excluded that the observed effects are related to the pharmacodynamic action of capmatinib as a MET receptor inhibitor.

It is of note that rats appear to be more sensitive to the toxicity of capmatinib than mice or monkeys, as was also evidenced in the single dose toxicity studies. A potential CNS effect of capmatinib related to its pharmacological mode of action could not be ruled out from these studies. No signs of CNS toxicity or brain abnormalities were observed in cynomolgus monkey studies. The relevance of the CNS findings in rats to humans is unknown. In this regard, the absence of clinical CNS toxicity in patients is reassuring.

As for genotoxicity studies, capmatinib resulted negative in the genotoxicity test battery (Ames test, *in* vitro chromosomal aberration assay, and *in vivo* bone marrow micronucleus test). No carcinogenicity studies were conducted, in line with ICH S9 guideline.

In line with ICH S9 guideline (nonclinical evaluation for anticancer pharmaceuticals), no carcinogenicity studies are required in the case of advanced cancer.

In embryo foetal development studies in rats and rabbits, capmatinib was teratogenic and fetotoxic at dose levels not eliciting maternal toxicity. In rats, decreased foetal weight and increased incidence of litters and foetuses with limb malformations were observed at the maternal exposure of ≥0.89 exposure multiples of the anticipated clinical exposure (based on the AUC). In rabbits, limb, lung and tongue malformations were seen at the maternal exposure of ≥0.025 exposure multiples of the anticipated clinical exposure.

In line with ICH guideline S9, neither fertility and early embryonic development nor pre- and postnatal toxicology studies have been conducted with capmatinib. There were no findings in reproductive organs in repeated dose toxicity studies in rats and monkeys. However, findings were reported in prostate after 4 weeks of administration in an impurity qualification study (no dose response in either weight changes or in the incidence and severity of histopathological changes were observed).

No toxicity studies in juvenile animals were conducted as it is not intended to be used in paediatric patients (specific waiver from EMA-PDCO).

In vitro and in vivo photosensitisation assays with capmatinib suggested that capmatinib has the potential for photosensitisation. Although there is considerable accumulation in the eye (lens), and the fact that capmatinib has photosensitizing activity as reported in the toxicology section, further studies concluded no relevance for the human situation.

No evidence of ototoxicity was observed.

Environmental Risk Assessment

Capmatinib is not a PBT substance.

Considering the above data, capmatinib is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the information submitted is considered adequate.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 11. Overview of studies with a clinical pharmacology component in healthy subjects included in the current application

Study code	Study type	Study description	Study population (number of subjects exposed to capmatinib)	Capmatinib formulation/ (orally)
[Study X2103]	Relative bioavailability capsule vs. tablet	Randomized, open-label, two-sequence, two-period, crossover study evaluating the relative bioavailability of capmatinib between capsule and tablet following a single oral dose of capmatinib in healthy subjects (fasting)	Healthy subjects (N = 24)	Single dose of capmatinib 600 mg tablet (3x200) and capsule (12x50)
[Study X2106]	Human ADME	Open-label study to investigate the absorption, distribution, metabolism and excretion (ADME) of capmatinib after a single oral dose of 600 mg [14C]*capmatinib 5.55 MBq) in healthy male subjects	Healthy subjects (N = 6)	Single dose of capmatinib capsule 600 mg
[Study X2107]	Food effect	Randomized, single-center, open-label, three-period, six-sequence, crossover study to investigate the effect of food on the PK of capmatinib following a single oral dose of 3 × 200 mg film-coated tablets in healthy subjects	Healthy subjects (N = 24)	Single dose of 600 mg capmatinib tablets (3 ×200 mg)
[Study A2101]	DDI with proton pump inhibitor	Single-center, open-label, two-period, single sequence study to assess the effect of rabeprazole on the PK of a single dose of capmatinib in healthy subjects	Healthy subjects (N = 20)	Single dose of 600 mg (3 × 200 mg) capmatinib tablets
[Study A2102]	DDI with itraconazole and rifampicin	Phase I, open-label, two arm drug-drug interaction study to assess the effect of itraconazole	Healthy subjects (N = 53)	Single dose of capmatinib

		(a CYP3A inhibitor) and rifampicin (a CYP3A inducer) on the PK of a single dose of capmatinib in healthy subjects	Inhibition Cohort (N = 27) Induction Cohort (N = 26)	tablet: 200 mg and 400 mg
[Study A2106]	Hepatic impairment	Open-label, single-dose, multicenter, parallel-group, two-staged study to evaluate the PK of capmatinib in non-cancer subjects with impaired hepatic function and noncancer subjects with normal hepatic function	(N = 31) Healthy subjects (N = 10), and hepatic impaired subjects (N = 21)	Single dose of capmatinib tablet: 200 mg
[Study A2109]	Bioequivalence for 150 mg tablet	Phase I, randomized, open label, three-period, six sequence crossover study to evaluate the bioequivalence of two batches of capmatinib 150 mg tablet (2x150 mg) in comparison to capmatinib 100 mg tablet (3x100 mg) following a single oral dose of 300 mg in healthy subjects (fasting)	Healthy subjects (N = 77)	Single dose of Capmatinib tablet: 300 mg
ADME: absorption, distribution, metabolism, and excretion; PK: pharmacokinetics; DDI - Drug-Drug Interaction				

Table 12. Overview of studies with a clinical pharmacology component in subjects with cancer included in the current application

Study code	**Study description**	**Study population (number of subjects exposed to capmatinib)**	**Capmatinib formulation and dosing (orally)**
[Study A2201] **PIVOTAL STUDY**	Phase II, multicenter, study of oral MET inhibitor capmatinib in adult subjects with EGFR wild-type, advanced non-small cell lung cancer	Subjects with EGFR wild type (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-negative rearrangement, advanced (stage IIIB or IV) NSCLC harboring MET mutations, and/or MET amplification) (N = 373)	Tablet 400 mg twice daily (capmatinib 100mg, 150mg and 200mg tablets) Down titration: 400mg =2x200mg 300mg =200mg+100mg or 3x100mg or 2x150 mg 200mg =200mg
[Study X1101]	Phase I open-label dose escalation study with a capmatinib maximum tolerated dose (MTD) dose-expansion phase in adult Japanese subjects with advanced solid malignancies	Japanese subjects with advanced solid tumors (N = 44)	Dose escalation arm: Once a day regimen with capsule: 100 mg, 200 mg, 400 mg, 500 mg, 600 mg, 800 mg twice daily regimen with capsule: 400 mg, 600 mg Tablet: 200 mg, 400 mg twice daily
[Study X2101T]	Phase I open-label dose escalation study to determine the safety, tolerability, PK and pharmacodynamics of capmatinib in subjects with advanced solid malignancies	Subjects with advanced solid malignancies (N = 45)	Dose escalation arm: Once daily regimen with capsule: 10 mg, 20 mg, 50 mg, 70 mg, 150 mg, 200 mg, 300 mg, 400 mg twice daily regimen with capsule: 50 mg, 200 mg, 300 mg
[Study X2102]	Phase I open-label dose escalation study with expansion to assess the safety and tolerability of capmatinib in subjects with	Subjects with MET dysregulated advanced solid tumors (N = 131)	Dose escalation arm (capsule): 100 mg, 200 mg, 250 mg, 350 mg, 450 mg, 600 mg all twice daily

	c-MET dysregulated advanced solid tumors (fasting)		Dose expansion arm (capsule): 600 mg twice daily Safety Cohort tablet: 400 mg tablet twice daily Dose expansion arm (tablet): 400 mg twice daily
[Study A2103]	Phase I, multicenter, open label, single-sequence drug drug interaction study to assess the effect of capmatinib on the PK of midazolam and caffeine in subjects with METdysregulated advanced solid tumors	Subjects with MET dysregulated advanced solid tumors (N = 37)	Tablet 400 mg twice daily
[Study A2105]	Phase I, multicenter, openlabel, single-sequence drug drug interaction study to assess the effect of capmatinib on the PK of digoxin and rosuvastatin in subjects with METdysregulated advanced solid tumors	Subjects with MET dysregulated advanced solid tumors (N = 31)	Tablet 400 mg twice daily
[Study A2108]	Phase I, multicenter, open label dose escalation study to evaluate the PK, safety, and tolerability of capmatinib tablet formulation with food in subjects with MET dysregulated advanced solid tumors	Subjects with MET dysregulated advanced solid tumors (N = 35)	Dose escalation tablet: 300 mg (N = 8) and 400 mg (N = 12) twice daily Expansion Phase twice daily dosing- tablet: 400 mg (N = 15) twice daily

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetic (PK) and biopharmaceutic properties of capmatinib were characterized in 7 Phase I studies in healthy subjects and 7 Phase I & II studies conducted in subjects with advanced solid tumours (see Table 11 and Table 12 above). Further, a population PK study was conducted, which included pharmacokinetic data from four clinical studies (X1101, X2102, A2108 and the pivotal Study A2201). The popPK analysis dataset included 3882 PK observations from 501 subjects and was used to explore the effect of covariates, predict PK concentrations and provide PK exposure metrics for exposure-response analyses.

To investigate the metabolism, the active transport, protein binding and the drug interaction potential of capmatinib and its major (inactive) metabolite CMN288, 37 in vitro studies were conducted. Further, PBPK models were used to evaluate the DDI potential of capmatinib with moderate CYP3A inhibitors and inducers.

Methods

Single dose and multiple dose pharmacokinetic studies were conducted, studies had an appropriate design. In the comparative single dose studies, a washout period of at least 7 days between each dose was implemented. Standard pharmacokinetic parameters were analysed (AUC_{last}, AUC_{inf}, C_{max} and T_{max}, AUC_{0-12}, lambda_z, $T_{½}$, MRT, CL/F and, Vz/F) and appropriate statistical methods were used.

Analytical methods

Two bioanalytical sites were used in the clinical development programme of capmatinib. The validated assay range for INC280 was 1.00-1000 ng/mL and 1.04 -1040 ng/mL at Wuxi Shanghai, China and at Wuxi, New Jersey, (USA), respectively. The bioanalytical methods were validated successfully at each site and were cross-validated. All clinical study samples were analysed within the demonstrated stability period of 674 days (INC280 and CMN288) or 875 days (INC280) in spiked plasma at ≤-70 ºC.

The in-study validations of all clinical studies show acceptable calibration standards and QCs for INC280 and CMN288 in human plasma. In addition, the in-study validations for measuring of rifampicin, itraconazole, midazolam, 4-Beta-Hydroxycholesterol, rosuvastatin and digoxin in human plasma also show acceptable calibration standards and QCs.

According to the Guideline on bioanalytical method validation the incurred sample re-analysis was performed in pivotal bioequivalence trials, in clinical trial in subjects, in patient trial and in trial in patients with impaired hepatic and/or renal function. In all cases, the results showed that greater than 80% of the ISR measurements in all ISR submitted were within ±20 %.

Absorption

In humans, absorption is rapid after oral administration of capmatinib. Peak plasma levels of capmatinib (C_{max}) were reached approximately 1 to 2 hours (t_{max}) after an oral 400 mg dose of capmatinib tablets in cancer patients. Under fed conditions, Tmax is approximately 4 to 6 hours. The absorption of capmatinib tablets after oral administration is estimated to be greater than 70%.

The popPK predicted steady state $AUC_{0\text{-}12h}$, C_{max}, and C_{min} (ng/ mL) are summarized in table below, for the 400 mg tablet BID only. No model based simulations were provided for the 300mg BID and 200mg BID dose level.

Table 13 Simulated steady state PK parameters for 400 mg tablet BID (A2201) population PK report

PARAMCD	n	mean	std	GeoMean	GeoCVp	median	min	max	CVp
AUC	310	25573.8273	11113.1708	23385.50	66.56	23953.76	4014.35	77242.70	43.46
CMAX	310	5630.4160	2075.1073	5261.83	65.20	5322.91	879.26	15023.63	36.86
CTROUGH	310	722.3064	653.9676	533.88	82.36	562.42	42.84	4762.21	90.54
TMAX	310	NA	NA	NA	NA	1.00	1.00	7.00	NA

/view/hoyu2_view/vob/CINC280X/pool/pkpd_002/nonmem/pgm/Task07_SSPKSumByCov.R
/view/hoyu2_view/vob/CINC280X/pool/pkpd_002/nonmem/results/Task06_run318_A2108simPKsum.pdf

Bioavailability

No absolute bioavailability study was conducted.

In the ADME study (**X2106)**, the fraction absorbed was estimated to be 49.6%, which was based on the percentage of radiolabelled dose recovered in urine and in faeces as metabolites following a single oral dose of 600 mg of [14C] capmatinib. As a capsule formulation was used in the ADME study and a considerable formulation effect was observed (administration of the tablet resulted in ≈1.5 fold higher exposure in patients and ≈2-fold higher exposure in healthy subjects, see capsule vs tablet).

Bioequivalence

Formulations used during the clinical development of capmatinib

The to-be-marketed formulations are Tabrecta 150 mg and 200 mg **film-coated tablets**. During the clinical development an early **capsule formulation** has been used in several clinical studies (ADME study **X2106** and dose escalation studies **X110, X2101T**, and **X2102**). Further, different tablet strengths have been tested during clinical development (capmatinib 100 mg, 150 mg and 200 mg tablets), the 100 mg strength will not be marketed.

Tablets vs. capsules

Study X2103 was conducted to compare the relative bioavailability of the film-coated tablets and the capsule formulation. Treatment with tablets provided higher systemic exposures (C_{max} and AUC) and lower variability compared with capsules. Geometric mean ratios (tablets to capsules) of the AUC_{last} and C_{max} were 2.37 (90% CI: 1.91, 2.93), and 3.01 (90% CI: 2.29, 3.95), respectively. There was greater variability in capsule (Treatment A) exposure than in tablet (Treatment B) exposure; e.g., the geometric CV% of capsules (Treatment A) for AUClast was approximately 82%, while that of tablets (Treatment B) was approximately 34%].

To match with the exposure for the 600 mg b.i.d. capsule, the tablet was introduced into patient studies at a dose of 200 mg b.i.d. based on the exposure ratio from the relative bioavailability study. However, the relative bioavailability between the FMI (final market image) tablet and capsule formulation was estimated to be ~1.5 in subjects with cancer. As subsequently observed, the $AUC_{tau,ss}$ from the 400 mg FMI tablet b.i.d. (geo-mean, geo-CV%: 21000 ng*h/mL, 59.6%) from pivotal Study A2201 was comparable to the exposure of the 600 mg capsule twice daily (geomean, geo-CV%: 21000 ng*h/mL, 68.0%) in Study X2102.

The low absorption of the capsules can probably be explained by the quality characteristics of the early capsule formulation. In the quality documentation, it is stated that the dissolution of capsules is slow or incomplete. This is because after the capsule shell disintegration, the capsule content forms a large agglomerate, which does not further disintegrate due to the API tendency to form a gel in aqueous media with pH ≤ 3.0. For this reason, the applicant decided to switch to a tablet formulation.

Clinical trial tablets vs To-be marketed tablets

In the pivotal study A2201, capmatinib film-coated tablet dose strengths of 100 mg and 200 mg were extensively studied to evaluate the safety and efficacy in subjects. The 200 mg batches (1010009729, 1010011116, X004 0115 and X094 0415) used in the pivotal study (A2201) had the same formulation as intended for the marketing, with minor differences of the coloured film-coating. The 100 mg tablet will not be marketed. Instead, a 150mg tablet has been developed to facilitate a dose reduction to 300 mg bid, when necessary, to assist in compliance.

In the pivotal study **A2201**, the subjects on 300 mg bid received (3×100 mg) or (1×100 mg + 1×200 mg) capmatinib film-coated tablets.

The relative bioavailability between 2×150 mg tablets and 3×100 mg capmatinib was evaluated in study **A2109**. Two different batches of the 150 mg tablet (with different manufacturing settings and different in vitro dissolution profiles) were tested. Bioequivalence was demonstrated for Test 1 (batch number 1010012759), when a single dose of 300 mg capmatinib administered as 2×150 mg tablets in comparison to 3×100 mg tablets in healthy subjects (AUC_{inf}: 0.984 (95% CI: 0.921, 1.05) C_{max}: 0.971 (95% CI: 0.887, 1.06)). Test 2 (batch number 1010011115) and Reference were not bioequivalent. The manufacturing settings of Test 1 were selected for the to-be-marketed 150 mg and 200mg formulation

No comparison was made between the 2×150 mg tablets and 1×100 mg + 1×200 mg capmatinib.

Influence of food

Solubility of capmatinib is pH-dependent. Solubility of capmatinib is high at pH 1.0 (> 5 mg/mL) and low (approximately 0.002 mg/mL) at pH 6.9 and pH 7.4. As presence of food can alter gastric pH, gastric emptying, gastrointestinal motility and bile secretion and may also affect oral absorption of a weak base, the potential food effect on the extent of absorption has been tested in food-effect study (**X2107**) with the tablet formulation (3 ×200 mg). A trend of exposure increase was observed when a single dose of capmatinib (600 mg) was given from under fasting to low fat and to high fat meal intake, suggesting a positive food effect on AUC. Exposure (AUC_{inf}) after a low fat meal was approximately 20% higher than that under fasting conditions. Exposure (AUC_{inf}) after a high fat meal was approximately 46% higher than that under fasting conditions. Maximum concentration (C_{max}) was 11% higher after a low fat meal and 15% higher after a high fat meal than that under fasting conditions. When capmatinib was administered at 400 mg twice daily in cancer patients, exposure (AUC0-12h) was similar after administration of capmatinib with food and under fasted conditions.

In the population PK analyses, food reduced bioavailability of capmatinib by about 13%, which is not considered clinically relevant. In addition, the estimated food effect might have been confounded by the Proton pump inhibitor (PPI) usage (see section on drug-drug interactions).

Distribution

The apparent distribution volume of capmatinib was moderate to high (Vz/F of 144 L to 1570 L). The apparent mean volume of distribution at steady state (Vss/F) is 164 litres in cancer patients. The blood to plasma ratio was 1.5 (concentration range of 10 to 1000 ng/ml), but decreased at higher concentrations to 0.9 (concentration 10000 ng/ml), indicating a saturation of distribution into red blood cells. Capmatinib is 96% bound to human plasma proteins, independent of concentration.

Elimination

Capmatinib-related radiolabeled material was excreted mainly with the feces in the range between 66.6% and 92.7% of the dose (mean = 77.9%) and in urine between 8.9% and 31.5% (mean: 21.8%) within 7 days (168 h). Unchanged capmatinib in urine was only detected in traces. Recovery of the radioactive dose from the excreta was complete at 7 days after dosing (mean = 99.7% of the dose; range: 94.8-104.1%).

The geometric mean apparent plasma terminal half-life (t1/2) ranged from 3.5 to 6.3 h across dose levels following once daily (q.d.) dosing in subjects. The effective half-life following 400 mg twice daily dosing (b.i.d.) with tablets was 6.54 h calculated based on the geometric mean accumulation ratio. The geometric mean steady state apparent oral clearance (CLss/F) was 19.8 L/h (geo CV%: 60.5%).

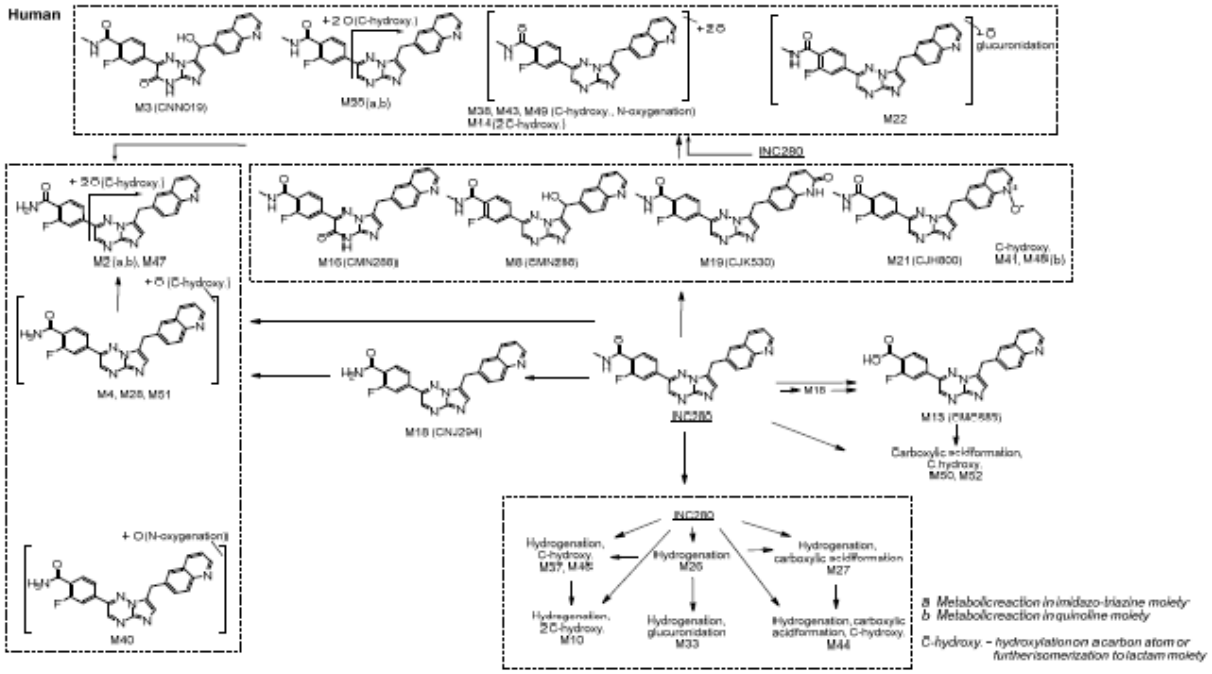
The elimination of capmatinib was investigated in the ADME study, using a capsule formulation. In faeces, capmatinib was the major component, accounting for 42.1 ± 23.0% of the dose, mainly as unabsorbed drug. Excretion of unchanged capmatinib in urine is negligible. As the bioavailability of capmatinib was formulation dependent and the estimated bioavailability of the tablets is 75-100%, the faecal excretion of the unabsorbed fraction following administration of the to-be-marketed tablet is expected to be lower and the fraction absorbed is anticipated to be higher.

Metabolism

In vitro and in vivo studies indicated that capmatinib is cleared mainly through metabolism driven by cytochrome P450 (CYP) 3A4 (40-50%) and aldehyde oxidase (40%). The biotransformation of capmatinib occurs essentially by Phase I metabolic reactions including C hydroxylation, lactam formation, N oxidation, N dealkylation, carboxylic acid formation, and combinations thereof. Phase II reactions

involve glucuronidation of oxygenated metabolites. The most abundant radioactive component in plasma is unchanged capmatinib (42.9% of radioactivity AUC0-12h). The major circulating metabolite, M16 (CMN288), is pharmacologically inactive and accounts for 21.5% of the radioactivity in plasma AUC0-12h.

Figure 1. Pharmacokinetics: Possible metabolic pathways in vivo in human



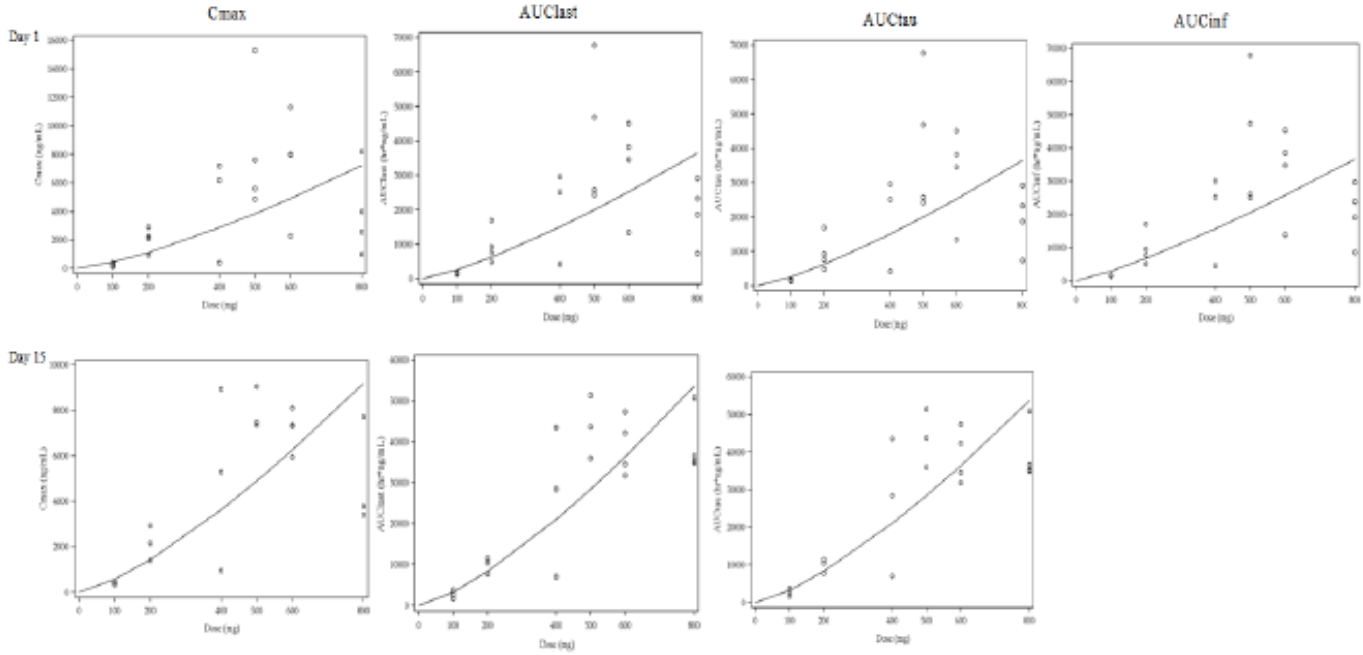
Once absorbed, capmatinib is extensively metabolised. The human ADME study and in vitro phenotyping results indicated that capmatinib was mainly metabolised by CYP3A4 and aldehyde oxidase (AO). The estimated fraction of metabolism through CYP3A4 is 40-50% and metabolism through AO is up to 40% based on ADME data. Six different metabolites (M16 (CMN288) 21.5%; M8 5.4%; M28 5.9%: M18 <3%; M26 <3%; M13 <3%) were identified, none of these metabolites is contributing to the pharmacological activity based on the limited amount formed and their IC50 values (see Table 14). Aldehyde oxidase was mainly responsible for the formation of M16 and M19.

Table 14 Pharmacological activity of capmatinib metabolite in plasma

Compound	Kinase assay, IC50 (nM)	Cellular assay, IC50 (nM)	%Relative to total radioactivity AUC0-12h in plasma	% in circulation relative to capmatinib AUC0-12h in plasma	Contribution to activity relative to capmatinib (%)
Capmatinib	1.7	3.5	42.9	NA	NA
M8 (CMN290)	36.5	181	5.4	13.1	0.3
M16 (CMN288)	> 10000	> 10000	21.5	49.3	0.0
M18 (CNJ294)	13	8.6	2.9	7.3	3.0

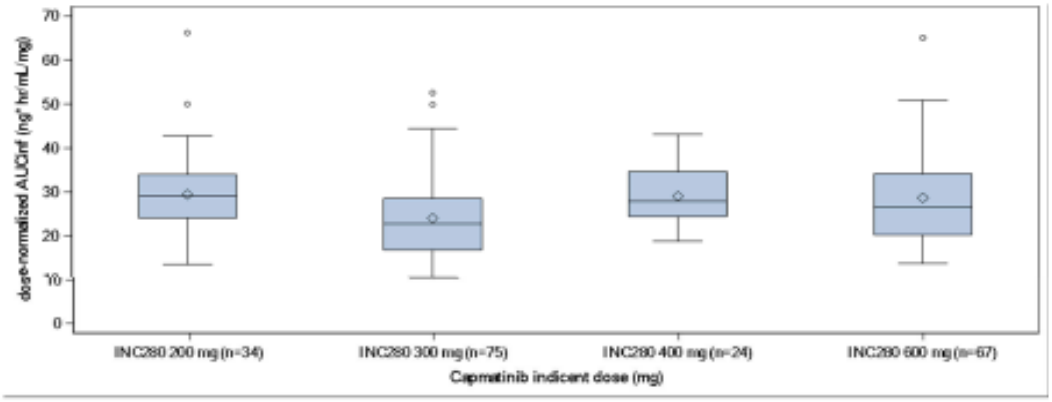
Dose proportionality and time dependencies

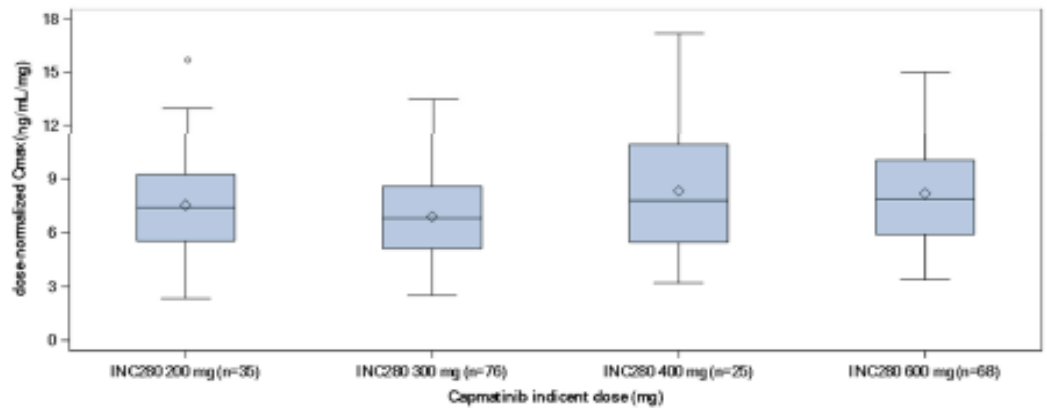
Figure 2: Dose proportionality following single dose in Study X1101



The solid line is PK parameter = exp(alpha)*dose**beta.

Figure 3: Boxplot of dose-normalised AUCinf and Cmax by incident dose-healthy volunteers (pharmacokinetic analysis set)





Capmatinib exhibited dose proportional increases in systemic exposure (AUCinf and Cmax) across the dose range tested (200 to 400 mg twice daily). Steady-state is expected to be achieved after

approximately 3 days after oral dosing of capmatinib 400 mg twice daily, with a geometric mean accumulation ratio of 1.39 (coefficient of variation (CV): 42.9%).

Time dependency

Based on population PK steady state appeared to have been reached by 3 days after b.i.d. dosing and the accumulation ratio is approximately 1.22. Based on data of pivotal study A2201, an accumulation ratio of 1.39 was calculated. These data consistently show low accumulation. No time dependency was observed.

Intra- and inter-individual variability

Using simulations of the population pharmacokinetic model, interindividual variability (Coefficient of Variation) of Cmax and AUCtau was estimated to be 38% and 40%, respectively. Intraindividual variability is approximately 43%.

The absorption and clearance are both highly variable. The overall variability in exposure was lower when capmatinib was given with food.

Pharmacokinetics in target population

Target population

The pharmacokinetics of capmatinib has been characterised in seven multiple dose studies in subjects with advanced solid tumours and seven, single dose studies, in healthy volunteers. The population pharmacokinetic model only included patient studies.

A population PK model-based simulation was performed to derive the PK parameters in subjects with cancer at 400 mg b.i.d. with tablets using the pivotal Study A2201 population. The predicted geometric mean steady-state C_{max} was 5262 ng/mL, in good agreement with the observed maximum concentration of 4780 ng/mL on Cycle 1 Day 15 in Study A2201, and occurred at similar t_{max}. The predicted geometric mean steady-state AUC_{0-12h} was 23386 h*ng/mL, also in agreement with the observed steady-state AUC_{0-12h} (20200 ng*h/mL) on Cycle 1 Day 15.

Base structural PK model

The popPK model was coded with parameters ALAG1 (time delay for absorption, h), D1 (duration of absorption, h), V1 (volume of central compartment, L), Q (intercompartmental clearance, L/h), V2 (volume of peripheral compartment, L), and CL (clearance from central compartment, L/h) and F1 (relative bioavailability). Since the pooled studies used different formulations and the medication was administered under different food conditions, formulation and food status were evaluated as covariates for ALAG1, D1 and F1 in the base model.

Table 15. PopPK parameters estimates – Base model

Parameter (unit)	Estimate	SE	RSE (%)	CV (%)	Shrinkage (%)
CL (L/h)	17.9	0.557	3.11		
V1 (L)	70.4	3.26	4.63		
ALAG1 (h)	0.059	0.006	10.17		
D1 (h)	1.01	0.055	5.45		
Q (L/h)	4.98	0.489	9.82		
V2 (L)	103	15.2	14.76		
Form~ALAG1	7.36	0.003	0.04		
Food~ALAG1	13.5	0.119	0.88		
Form~D1	1.7	0.094	5.53		
Food~D1	4.4	0.154	3.50		
Form~F1	0.701	0.065	9.27		
Food~F1	0.874	0.037	4.23		
ω^2_{CL}	0.244	0.023	9.43	52.57	8.94
$\omega^2_{CL\sim V1}$	0.187	0.025	13.37		
ω^2_{V1}	0.239	0.063	26.36	51.96	22.81
ω^2_{ALAG1}	1.19	0.144	12.10	151.23	42.40
$\omega^2_{ALAG1\sim D1}$	0.352	0.077	21.88		
ω^2_{D1}	0.62	0.102	16.45	92.68	37.66
ω^2_{Q}	1.09	0.185	16.97	140.51	32.36
$\omega^2_{Q\sim V2}$	1.52	0.213	14.01		
ω^2_{V2}	3.13	0.376	12.01	467.70	36.09
σ^2_{prop}	0.152	0.021	13.82		
$\sigma^2_{additive}$	36.4	12.3	33.79		

Model run number: run197.mod
RSE: relative standard error, calculated using SE/abs(Estimate)*100%.
Random effects and residual errors are expressed as variance.
Covariance~parameter indicates a parameter associated with covariate effect.
CV (%) was calculated using $\sqrt{e^{\omega^2} - 1} * 100\%$.
Shrinkage reported by NONMEM v7.3.

Figure 4. VPC for base model (capsule at 600 mg)

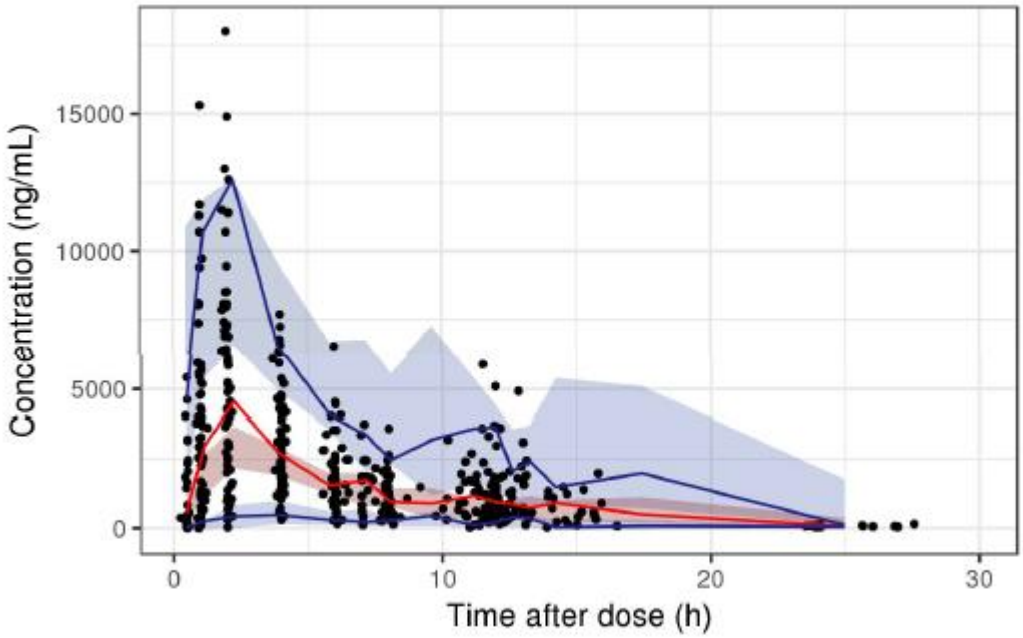
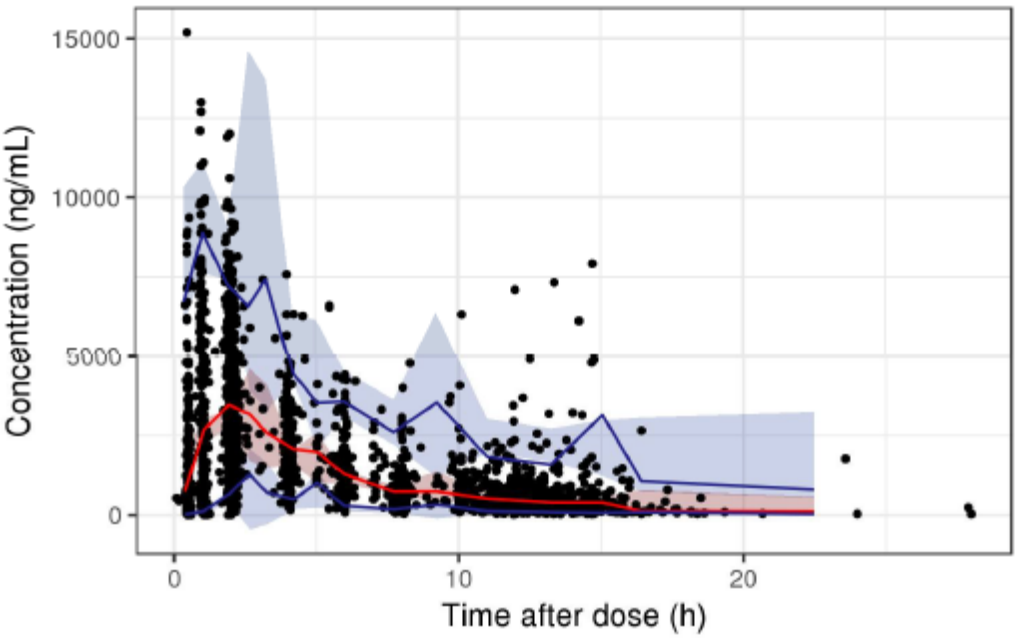


Figure 5. VPC for base model (tablet at 400 mg)



Final model

Table 16. PopPK parameters estimates – Final model

Parameter (unit)	Estimate	SE	RSE (%)	CV (%)	Shrinkage (%)
CL (L/h)	18.4	0.509	2.77		
V1 (L)	72.8	2.28	3.13		
ALAG1 (h)	0.049	0.005	10.20		
D1 (h)	0.918	0.047	5.12		
Q (L/h)	4.48	0.444	9.91		
V2 (L)	91.0	12.5	13.74		
Form~ALAG1	9.08	0.002	0.02		
Food~ALAG1	16	0.065	0.41		
Form~D1	1.92	0.095	4.95		
Food~D1	4.49	0.16	3.56		
Form~F1	0.649	0.041	6.32		
Food~F1	0.874	0.064	7.32		
Weight~CL	0.517	0.15	29.01		
Asian~CL	0.928	0.031	3.34		
Weight~V1	0.942	0.135	14.33		
ω^2_{CL}	0.223	0.020	8.97	49.98	8.87
$\omega^2_{CL\sim V1}$	0.16	0.021	13.13		
ω^2_{V1}	0.182	0.032	17.58	44.68	23.00
ω^2_{ALAG1}	1.18	0.142	12.03	150.15	43.34
$\omega^2_{ALAG1\sim D1}$	0.326	0.085	26.07		
ω^2_{D1}	0.719	0.135	18.78	102.59	40.62
ω^2_{Q}	1.32	0.221	16.74	165.63	31.93
$\omega^2_{Q\sim V2}$	1.71	0.257	15.03		
ω^2_{V2}	3.25	0.382	11.75	497.90	35.99
σ^2_{prop}	0.152	0.014	9.21		
$\sigma^2_{additive}$	31.6	13.4	42.41		

Model run number: run318.mod
RSE: relative standard error, calculated using SE/abs(Estimate)*100%.
Random effects and residual error are expressed as variance.
Covariance~parameter indicates a parameter associated with covariate effect.
CV (%) was calculated using $\sqrt{e^{\omega^2} - 1} * 100\%$.
Shrinkage reported by NONMEM v7.3.

Figure 6. VPC for final popPK model (capsule at 600 mg steady state)

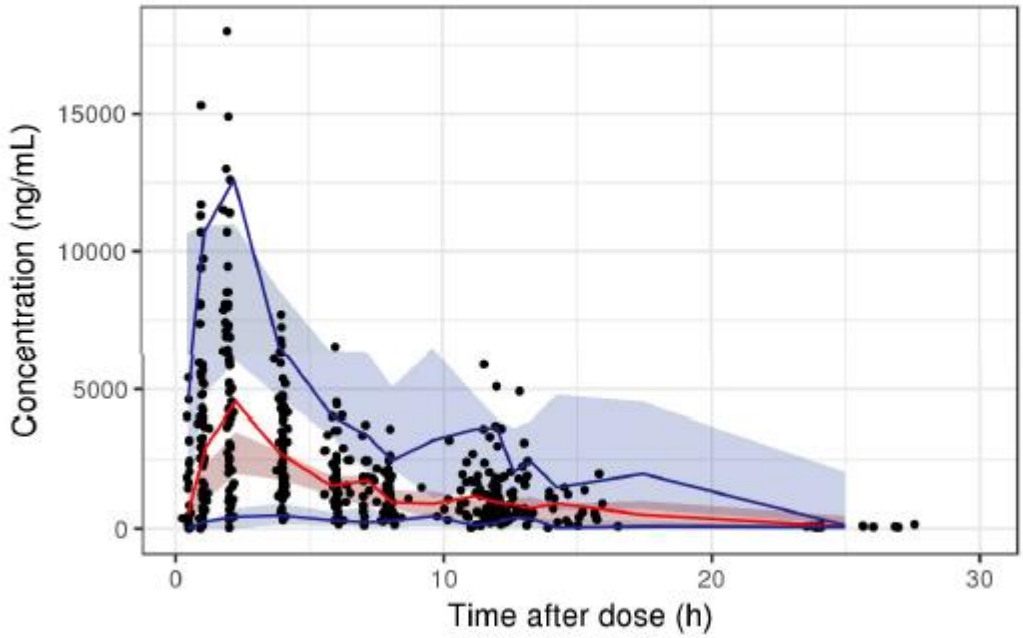


Figure 7. VPC for final popPK model (tablet at 400 mg)

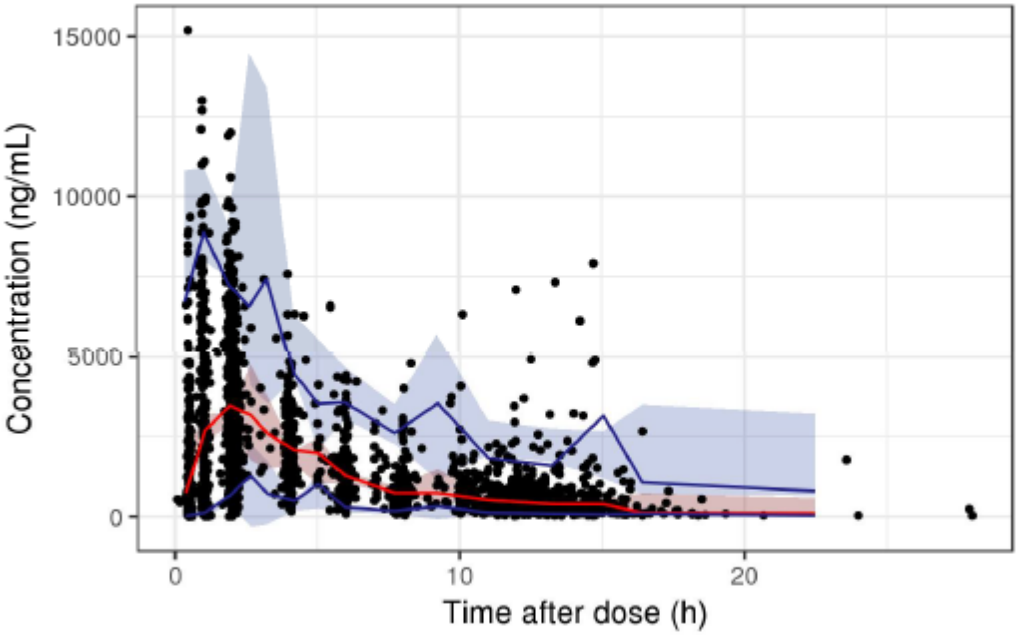


Table 17. Summary of ratio of steady state AUC, Cmax and Ctrough based on 500 simulated trials from A2201 patient population (full model 1)

	Ratio of AUCss (ng/mL*hr)			Ratio of Cmax,ss (ng/mL)			Ratio of Ctrough,ss (ng/mL)		
	Geo-mean	5%	95%	Geo-mean	5%	95%	Geo-mean	5%	95%
Age (reference: <65 years)									
≥65 years	1.05	0.95	1.17	1.05	0.96	1.16	1.07	0.88	1.28
Gender (reference: Male)									
Female	1.06	0.94	1.17	1.12	1.01	1.23	0.99	0.80	1.19
Weight (reference: 60-80 kg)									
<60 kg	1.17	1.03	1.32	1.23	1.08	1.40	1.13	0.90	1.41
>80 kg	0.87	0.76	1.00	0.82	0.72	0.93	0.92	0.73	1.17
Asian (reference: No)									
Yes	1.19	1.05	1.35	1.17	1.05	1.31	1.29	1.03	1.63
Japanese (reference: No)									
Yes	1.16	0.99	1.36	1.16	1.00	1.34	1.23	0.94	1.60
Hepatic function (reference: Normal)									
Impaired	1.07	0.87	1.28	1.06	0.89	1.25	1.10	0.79	1.56
Renal function (reference: Normal)									
Mild	1.08	0.96	1.23	1.12	1.01	1.26	1.05	0.86	1.29
Moderate	1.14	0.98	1.32	1.21	1.05	1.38	1.08	0.82	1.40
PPI* (reference: No)									
Yes	0.99	0.89	1.11	0.99	0.90	1.11	0.98	0.81	1.16

Ratio of steady state exposure was calculated as geometric mean (covariate category) / geometric mean (reference category).
*: A subject with any PPI usage during the study is grouped as PPI Yes; Otherwise PPI No.

Table 18. Summary of ratio of steady state AUC, Cmax and Ctrough based on 500 simulated trials from A2201 patient population (full model 2)

	Ratio of AUCss (ng/mL*hr)			Ratio of Cmax,ss (ng/mL)			Ratio of Ctrough,ss (ng/mL)		
	Geo-mean	5%	95%	Geo-mean	5%	95%	Geo-mean	5%	95%
Age (reference: <65 years)									
≥65 years	1.05	0.94	1.16	1.05	0.96	1.16	1.05	0.86	1.29
Gender (reference: Male)									
Female	1.06	0.94	1.19	1.11	1.00	1.23	0.98	0.79	1.21
Weight (reference: 60-80 kg)									
<60 kg	1.17	1.03	1.33	1.23	1.09	1.38	1.13	0.91	1.40
>80 kg	0.86	0.75	0.98	0.82	0.72	0.94	0.89	0.71	1.14
Asian (reference: No)									
Yes	1.10	0.98	1.24	1.13	1.01	1.26	1.10	0.89	1.37
Japanese (reference: No)									
Yes	1.10	0.93	1.28	1.13	0.98	1.29	1.08	0.80	1.43
Hepatic function (reference: Normal)									
Impaired	1.08	0.88	1.30	1.06	0.89	1.25	1.12	0.79	1.61
Renal function (reference: Normal)									
Mild	1.08	0.97	1.23	1.12	1.01	1.25	1.05	0.86	1.31
Moderate	1.14	0.97	1.34	1.21	1.05	1.39	1.08	0.80	1.44
PPI* (reference: No)									
Yes	1.00	0.90	1.12	1.00	0.90	1.11	0.99	0.83	1.19

Ratio of steady state exposure was calculated as geometric mean (covariate category) / geometric mean (reference category).
*: A subject with any PPI usage during the study is grouped as PPI Yes; Otherwise PPI No.

Special populations

Impaired renal function

Based on a population pharmacokinetic analysis that included 207 patients with normal renal function (creatinine clearance [CLcr] ≥90 ml/min), 200 patients with mild renal impairment (CLcr 60 to 89 ml/min), and 94 patients with moderate renal impairment (CLcr 30 to 59 ml/min), mild or moderate renal impairment had no clinically significant effect on the exposure of capmatinib. Tabrecta has not been studied in patients with severe renal impairment (CLcr 15 to 29 ml/min) (see sections 4.2 and 5.2 of the SmPC).

Impaired hepatic function

A study was conducted in non cancer subjects with various degrees of hepatic impairment based on Child Pugh classification using a 200 mg single dose of capmatinib. The geometric mean systemic exposure (AUCinf) of capmatinib was decreased by approximately 23% and 9% in subjects with mild (N=6) and moderate (N=8) hepatic impairment, respectively, and increased by approximately 24% in subjects with severe (N=6) hepatic impairment compared to subjects with normal (N=9) hepatic function. Mild, moderate or severe hepatic impairment had no clinically significant effect on the exposure of capmatinib (see sections 4.2 and 5.2 of the SmPC).

Hepatic impairment was classified based on Child Pugh classification and a confirmed history of hepatitis C, or histologically by prior liver biopsy showing cirrhosis, or clinically by physical examination (e.g. liver firmness to palpation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy, ascites, presence of asterixis or gynecomastia), or laboratory data, or liver imaging (computed tomography and/or ultrasound and/or magnetic resonance imaging scans) or endoscopic findings.

Gender, Race and Age

The effect of gender, race, and age have been evaluated using the population pharmacokinetic model. None of these covariates had clinical relevant effects.

Figure 8. Simulated covariate effects of renal impairment, hepatic, gender, ethnicity (Asian), BW and age on AUC, Cmax, Ctrough, CL and V1 (full model 1)

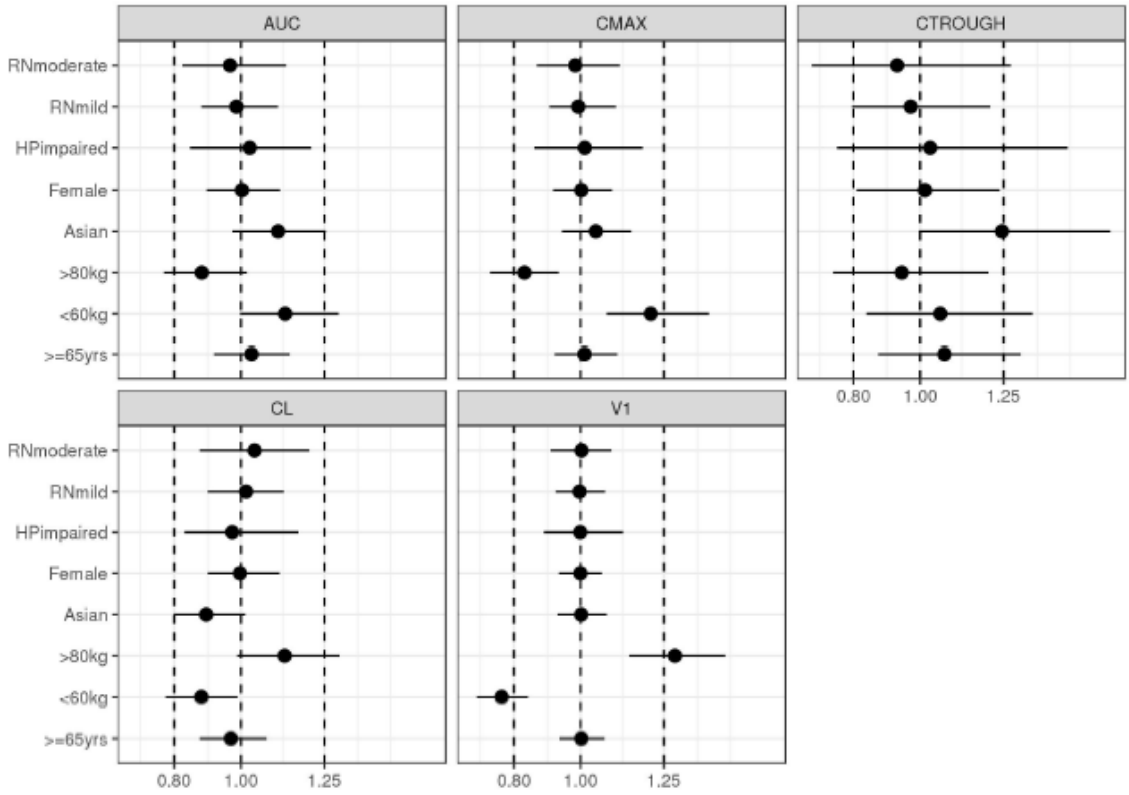


Figure 9. Simulated covariate effects of renal impairment, hepatic, gender, ethnicity (Japanese), BW and age on AUC, Cmax, Ctrough, CL and V1 (full model 2)

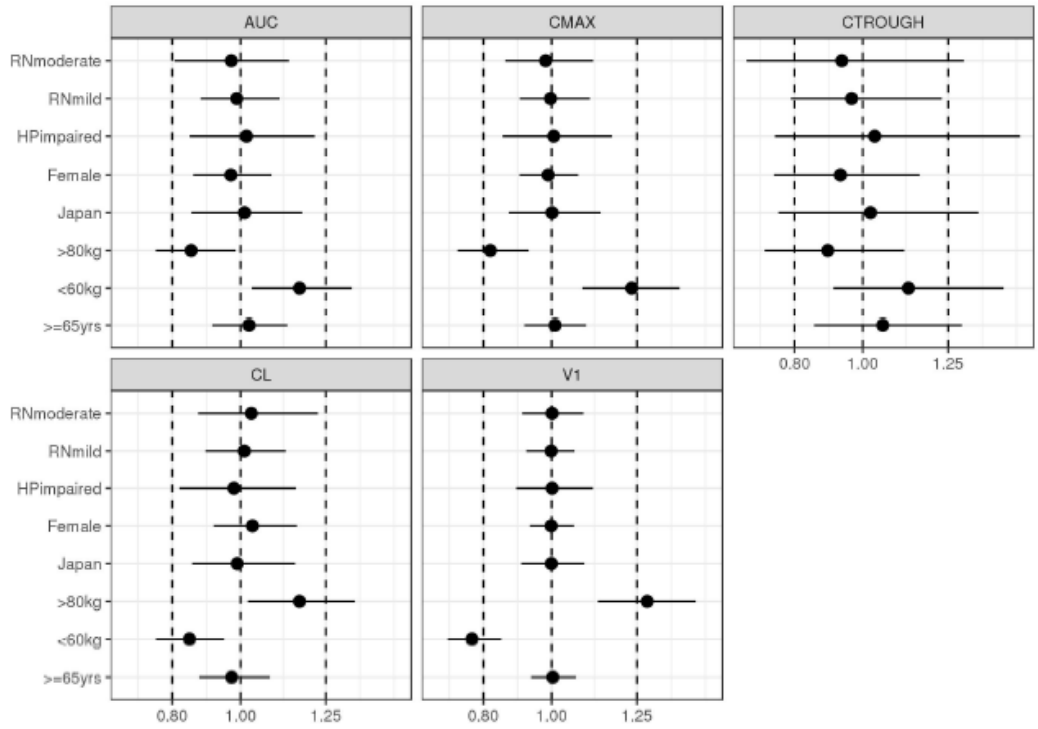


Table 19: Age distribution for popPK analysis set overall and by study

	Age < 65	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
popPK analysis set	266/501	178/501	50/501	7/501
A2201	136/310	123/310	44/310	7/310
A2108	22/35	1/35	12/35	0/35
X2102	80/112	27/112	5/112	0/112
X1101	28/44	16/44	0/44	0/44

Weight

Post-hoc comparison of AUC and C_{max} was performed using patients below 60 kg versus patients above 80 kg, which demonstrated that the AUC and C_{max} was significantly higher in patients with a bodyweight below 60 kg (28463 ng/mL.hr versus 18466.37, and 6646 versus 3923 ng/mL, respectively).

Pharmacokinetic interaction studies

In vitro / In silico

PBPK modelling

A physiologically-based pharmacokinetic (PBPK) model was built for capmatinib (Study 1701418), using the Simcyp® [1] population-based clearance and drug-interaction simulator. The PBPK model was

[1] Simcyp Population-based Simulator, Version 18 Release 1 (Certara Inc., Princeton, NJ)

developed to assess the DDI risk of capmatinib as victim (for inhibitors and inducers of CYP3A) and as perpetrator (with substrates of CYP2C8, CYP2C9, CYP2C19, and CYP2B6).

The PBPK Perpetrator model used the modified Simcyp Cancer Population and Simcyp library compound profiles for several inhibitor, inducer and substrate compounds. The modified cancer patients population is based on publication by (Schwenger et al. 2018[2]). A reduction in activity (or abundance) of CYP1A2, CYP2C19, and CYP3A4 by 20–33% was applied to better capture the PK of a subset of oncology compounds using Simcyp®. For the cancer patients with c-MET dysregulated tumours, the Simcyp Cancer Population file was further modified to include a 20% reduction in CYP3A4 abundance in the liver and intestine. This modified Simcyp Cancer population improved the prediction of the clearance of midazolam. No corrections were made for CYP1A2 activity as the concentration-time profiles of the CYP1A2 probe substrate, caffeine appeared to be well predicted.

CAPMATINIB AS VICTIM'S DRUG

Moderate CYP3A inhibitors and inducers

Using in vitro and in vivo parameters from non-clinical and clinical studies, a PBPK model was built and was optimized 'top-down' to refine the fmCYP3A4 value of capmatinib and interplay of the CYP3A4 induction and inactivation mechanisms. This was accomplished by adjustment of the CYP3A4 fm, Kapp (KI), and capmatinib fu(gut) values using clinical DDI data of the interaction of capmatinib with the strong CYP3A inhibitor, itraconazole, and sensitive CYP3A4 substrate, midazolam. The model predicted the single dose PK profiles and calculated PK parameters of capmatinib for doses of 200-600 mg in healthy volunteers with sufficient accuracy. With a modified Simcyp Cancer population model (20% reduction of CYP3A4 abundance), the single dose and multiple dose PK of capmatinib at a 400 mg b.i.d. dose in subjects with cancer was well predicted. This PBPK model was further verified against caffeine and rifampicin DDI study results (A2102 and A2103) to confirm the predictability.

Simulations using physiologically based pharmacokinetic (PBPK) models predicted that co administration of a 400 mg capmatinib dose with the moderate CYP3A inducer efavirenz (600 mg daily for 20 days) would result in a 44% decrease in capmatinib AUC0-12h and 34% decrease in Cmax at steady state compared to administration of capmatinib alone.

The prediction of effect of moderate CYP3A inhibitors, erythromycin and fluconazole, on the PK of capmatinib at 400 mg b.i.d. was carried out with the same cancer patient population. Dose used for erythromycin and fluconazole were 500 mg t.i.d. and 200 mg q.d., respectively. The model predicted a marginal inhibition effect of these two drugs with 22-25% increase of capmatinib AUC0-12h, and 14-16% increase in Cmax at the steady state

CAPMATINIB AS PERPETRATOR'S DRUG

Other CYP substrates

The Simcyp PBPK model and CYP-probe substrate compound files in Simcyp library were used to simulate the effect of capmatinib on CYP2C8, CYP2C9, CYP2C19 and CYP2B6 probe substrates as summarized in Table 20. Among four CYP isoform substrates, only CYP2C8 substrate repaglinide showed modest 23% increase in Cmax and 39% increase in AUCinf when co-administrated with capmatinib at 400 mg b.i.d. No significant exposure change was predicted for warfarin, omeprazole or bupropion. Therefore, capmatinib is predicted to be a weak inhibitor of CYP2C8, and not an inhibitor or inducer for CYP2C9, CYP2C19 or CYP2B6. The only known CYP2C8 substrate with narrow therapeutic index so far is paclitaxel,

[2] Schwenger E, Reddy VP, Moorthy G, et al (2018) Harnessing Meta-analysis to Refine an Oncology Patient Population for Physiology-Based Pharmacokinetic Modeling of Drugs. Clin Pharmacol Ther; 103(2):271-280.

which is unlikely to be given concomitantly with capmatinib. Therefore, the weak DDI between capmatinib and sensitive CYP2C8 substrate is not considered clinically relevant.

Table 20. PBPK model predicted exposure changes of CYP probe substrates (single dose on Day 6) by co-administration of capmatinib (400 mg b.i.d) in patients

CYP enzyme evaluated	Probe substrate	Geometric mean Cmax ratio (90% CI) (ng/mL)	Geometric mean AUCinf ratio (90% CI) (ng·h/mL)
CYP2C8	Repaglinide	1.23 (1.20, 1.25)	1.39 (1.35, 1.43)[1]
CYP2C9	Warfarin	1.01 (1.01, 1.01)	1.07 (1.06, 1.07)
CYP2C19	Omeprazole	1.10 (1.09, 1.10)	1.12 (1.11, 1.13)
CYP2B6	Bupropion	0.989 (0.986, 0.991)	0.984 (0.981, 0.987)

The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 37-75 years, and proportion of female 0.5. The population model used was the modified Simcyp Cancer Patient population. The probe substrate was given on Day 6 and capmatinib was given as a 400 mg b.i.d. dose on day 1- day 9 or Day 20 (for the Warfarin DDI simulation), details of the trial design can be found in [DMPK R1701418-Table 3-4].
[1]The value is the geometric mean AUClast value, as AUCinf was not outputted from the model.

Effect on transporters:

In vitro transport studies indicate that capmatinib inhibits the activities of multiple transporters including P-gp, BCRP, OATP1B1, OATP1B3, MRP2, BSEP, OAT1, OAT3, OCT2 and MATE1 and MATE2K.

Capmatinib inhibits P-gp in vitro with a Ki of 12.0 μM and has potential to inhibit P-gp at high luminal concentration in the intestine based on static DDI assessment, as Cgut is 324 fold higher than the Ki value.

Capmatinib inhibits BCRP in vitro with a Ki of 8.20 μM and has potential to inhibit BCRP at high luminal concentration in the intestine based on static DDI assessment, as Cgut is 474-fold higher than the Ki value.

In vitro, capmatinib showed inhibition of hepatic uptake transporter OATP1B1 and OATP1B3 with Ki of 6.5 and 6.2 μM, respectively

Capmatinib showed potent inhibition of renal transporter MATE1 and MATE2K with Ki of 0.28 and 0.29 μM, respectively [DMPK R1400238]. A high inhibition risk was indicated by Cmax,ss/Ki ratios of 1.66 and 1.60 in the static risk assessment using plasma capmatinib concentration.

In vivo

CAPMATINIB AS VICTIM'S DRUG

Capmatinib is a substrate for CYP3A4 and transporter P-gp. It is not a substrate of any hepatic uptake transporters.

CYP3A inhibitor and inducer

A clinical DDI study (Study A2102) was conducted to investigate the effect of itraconazole (a strong CYP3A inhibitor) and rifampicin (a strong CYP3A inducer) on the PK of a single dose of capmatinib in healthy subjects. Co-administration of a single 200 mg capmatinib dose with itraconazole (200 mg once daily for 10 days) increased capmatinib AUC_{inf} by 42% with no change in capmatinib C_{max} compared to administration of capmatinib alone. Rifampicin treatment (600 mg once daily × 9 days) resulted in a 67% decrease in capmatinib AUCinf and 56% decrease in Cmax.

Gastric pH-altering agents

In PK/safety Study A2108 when capmatinib was administered with food, 6 subjects with cancer were concomitantly administered PPI at the time of the PK evaluation. Compared to non-PPI users, the AUC0-12h for PPI-users were 38% lower and the Cmax was 44-46% lower on Day 1 and at steady state and.

Given the small sample size and parallel group comparison, the extent of decrease was considered similar to results observed in healthy subjects.

In healthy subjects (study A2101), co-administration of a single 600 mg capmatinib dose with the proton pump inhibitor rabeprazole (20 mg once daily for 4 days) decreased capmatinib AUCinf by 25% and decreased Cmax by 38% compared to administration of capmatinib alone. As capmatinib is a weak base with pH-dependent solubility this may possibly be explained by decreased solubility.

Given the modest effect of PPI observed in Study A2101, the effect of H2-receptor antagonists or antacids on capmatinib absorption was not evaluated. In Study A2201, H2-receptor antagonists and antacids were allowed, but with a recommended administration window relative to capmatinib administration.

CAPMATINIB AS PERPETRATOR'S DRUG

CYP3A4 substrates

Effect of capmatinib on the PK of sensitive CYP3A substrate, midazolam, was investigated in subjects with MET dysregulated advanced solid tumors (Study A2103). Multiple doses of capmatinib treatment at 400 mg b.i.d. resulted in a 22% increase in midazolam Cmax and a 9% increase in midazolam AUCinf. Therefore, capmatinib is unlikely to cause clinical DDI with CYP3A substrates.

CYP1A2 substrates

Effect of capmatinib on the PK of sensitive CYP1A2 substrate, caffeine, was investigated in subjects with MET dysregulated advanced solid tumors. Multiple doses of capmatinib treatment at 400 mg b.i.d. resulted in a 134% increase (GMR of 2.34 (2.08, 2.63) in caffeine AUCinf with no increase in caffeine Cmax, when compared to caffeine alone and (Study A2103).

P-gp substrates

A clinical study was conducted to assess the inhibitory potential of capmatinib on the PK of P-gp substrate digoxin in subjects with MET dysregulated advanced solid tumours (Study A2105). Compared to digoxin alone, capmatinib co-administration resulted in a 74% increase in digoxin Cmax and 47% increase in AUCinf.

BCRP substrates

A clinical study was conducted to assess the inhibitory potential of capmatinib on the PK of BCRP substrate rosuvastatin in subjects with MET dysregulated advanced solid tumors. Compared to rosuvastatin alone, capmatinib coadministration resulted in a 204% increase in rosuvastatin Cmax and 108% increase in AUCinf.

2.6.2.2. Pharmacodynamics

Mechanism of action

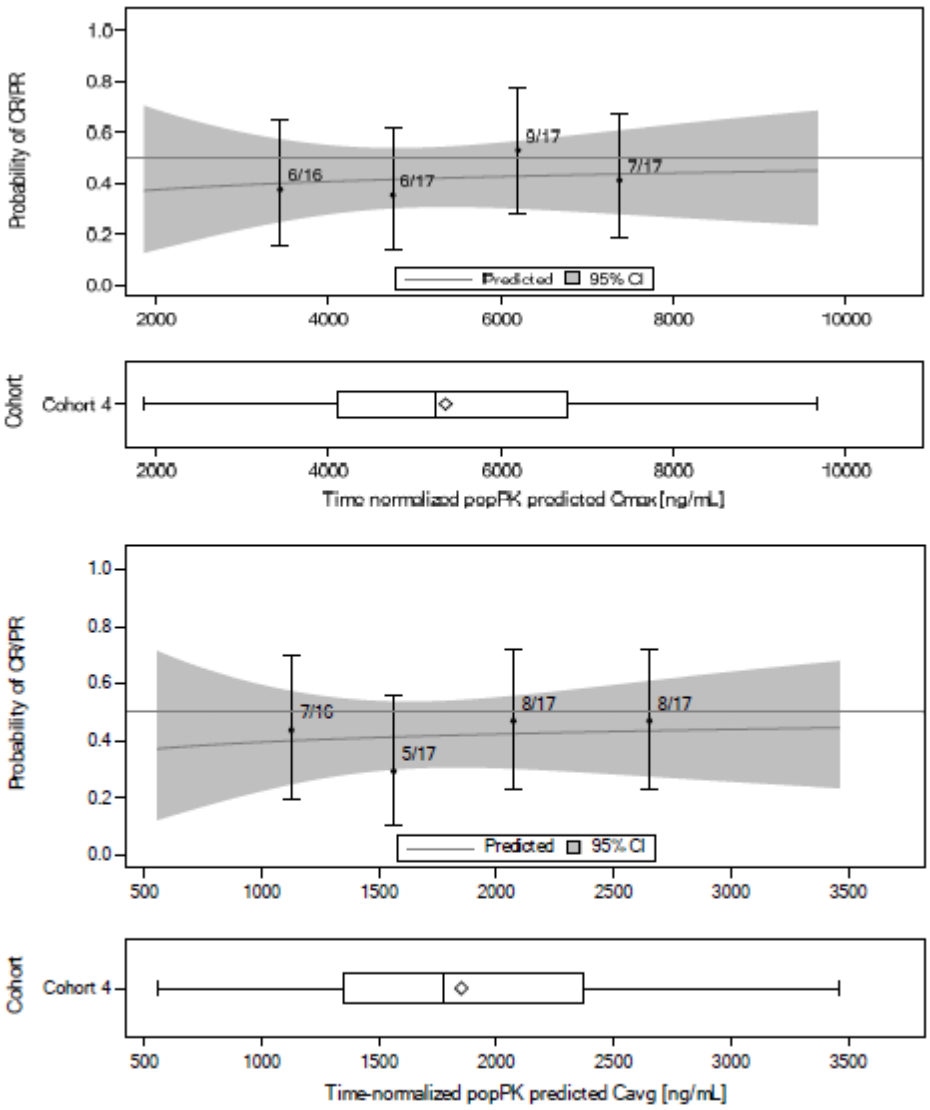
No mechanism of action studies have been submitted

Primary pharmacology

Exposure-efficacy

Best Overall Response (BOR)

Figure 10. Logistic regression of probability of BOR being CR or PR versus time-normalized popPK predicted Cmax and Cavg – A2201 MET mutant subjects (Cohort 4, 2/3L mutant) (PK-Efficacy set)



Model is log(p/(1-p)) = intercept + log time-normalized popPK predicted PK parameter, where p is the probability of BOR being CR or PR.

Boundaries are the 95% CI of the logistic regression model estimation.

The model estimates were generated at the median of baseline tumor size.

Duration of Response (DOR)

Table 21. Extended Cox regression model of DOR with time-normalized popPK predicted PK parameters between Study Day 1 and stop of response as covariate, by cohort – A2201 MET mutant subjects (PK-Efficacy set)

Cohort	Number of events / Patients at risk (%)	Prognostic variables	p-value	Change in exposure	Hazard ratio	95% CI
Cohort 4 (2/3L, MET mutant)	20/28 (71.4)	ECOG Status at Baseline	0.006	1 vs 0*	0.244	(0.089, 0.669)
		Log of Time-normalized popPK predicted Cavg [ng/mL]	0.966	50% increase	1.009	(0.661, 1.541)
				30% decrease	0.992	(0.684, 1.439)
				50% decrease	0.984	(0.477, 2.030)
		ECOG status at Baseline	0.010	1 vs 0*	0.265	(0.096, 0.728)
		Log of Time-normalized popPK predicted Cmax [ng/mL]	0.689	50% increase	0.911	(0.578, 1.436)
				30% decrease	1.085	(0.727, 1.619)
				50% decrease	1.172	(0.539, 2.550)
Cohort 5b (1L, MET mutant)	10/18 (55.6)	Log of Time-normalized popPK predicted Cavg [ng/mL]	0.885	50% increase	0.940	(0.407, 2.172)
				30% decrease	1.056	(0.505, 2.205)
				50% decrease	1.111	(0.266, 4.650)
		Log of Time-normalized popPK predicted Cmax [ng/mL]	0.491	50% increase	0.751	(0.332, 1.696)
				30% decrease	1.287	(0.628, 2.636)
				50% decrease	1.632	(0.405, 6.576)

The analysis includes only the subjects who had a response.

These are the patients at risk at the start of the response.

Event is the end of the response.

*For ECOG, this represents the ratio for baseline ECOG PS of 1 vs. baseline ECOG PS of 0.

Source: Appendix-Table 3-9

Among the covariates tested, only ECOG performance status was retained in the final model for Cohort 4 (Appendix - Table 3-9a). The model for Cohort 4 suggested a higher benefit on DOR in subjects with an ECOG of ≥1 at baseline compared to those with an ECOG of 0. This result should be interpreted with caution given the small number of responders with ECOG performance status of 0 in Cohort 4 (n=8, [Study A2201 - Table 14.2-1.7-4]).

Progression Free Survival (PFS)

Table 22. Extended Cox regression model of PFS with time-normalized popPK predicted PK parameters as covariate – A2201 MET mutant patients (Cohort 4, 2/3L mutant) (PK-Efficacy set)

Table 4-4 Extended Cox regression model of PFS with time-normalized popPK predicted PK parameters as covariate – A2201 MET mutant patients (Cohort 4, 2/3L mutant) (PK-Efficacy set)

Cohort	Number of events / Patients at risk (%)	Prognostic variables	p-value	Change in exposure	Hazard ratio	95% CI
Cohort 4 (2/3L, MET mutant)	55/67 (82.1)	Log of Baseline Tumor Size	0.004	50% increase*	1.334	(1.099, 1.621)
		Log of Time-normalized popPK predicted Cmax [ng/mL]	<0.001	50% increase	0.636	(0.492, 0.823)
				30% decrease	1.489	(1.187, 1.868)
				50% decrease	2.167	(1.394, 3.367)
		Log of Baseline Tumor Size	0.007	50% increase*	1.299	(1.076, 1.570)
		Log of Time-normalized popPK predicted Cavg [h*ng/mL]	0.003	50% increase	0.691	(0.541, 0.882)
				30% decrease	1.385	(1.117, 1.717)
				50% decrease	1.883	(1.239, 2.860)

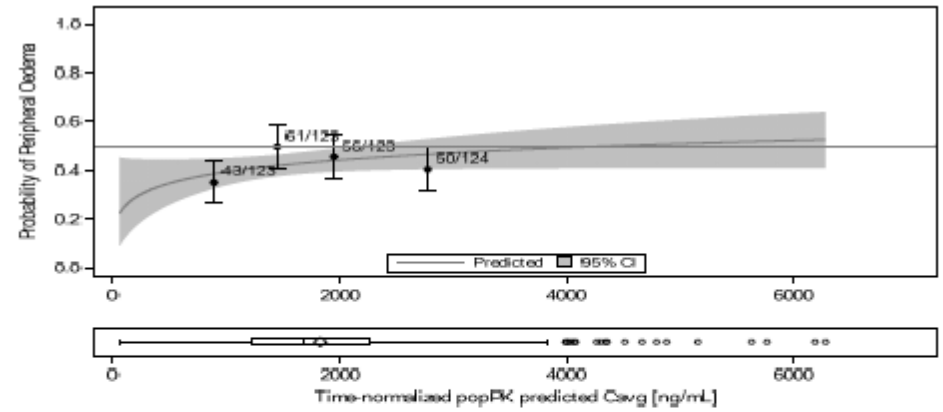
Source: Appendix-Table 3-10

* This represents the ratio for an increase of 50% in baseline tumor size.

Exposure-safety

Probability of peripheral oedema events

Figure 11. Probability of peripheral oedema events



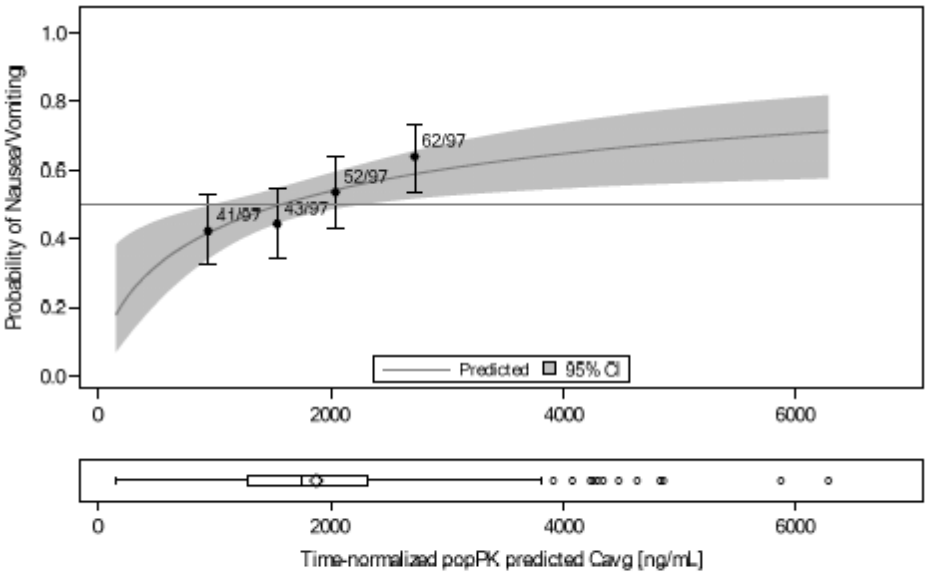
Model is log(p/(1-p)) = intercept + log time-normalized popPK predicted PK parameter, where p is the probability of AE.

Boundaries are the 95% CI of the logistic regression model estimation. The dots are the observed proportions in each time-normalized popPK predicted PK parameter quartile. The 95% CIs for these are based on the Clopper-Pearson method.

Diamond represents the mean and circle represents values outside of 1.5*IQR. Lower and upper whiskers extend to the most extreme points within 1.5*IQR of Q1 and Q3 respectively.

Probability of nausea/vomiting events

Figure 12. Probability of nausea / vomiting events



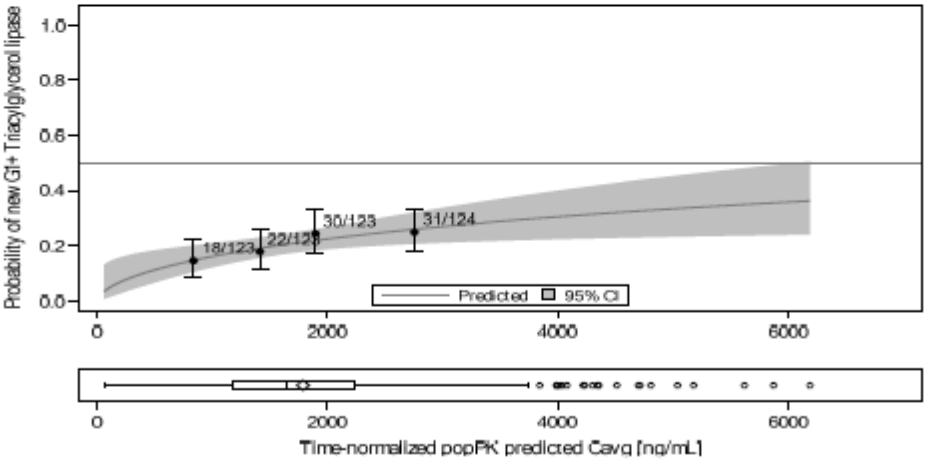
The dots are the observed proportions in each time-normalized popPK predicted PK parameter quartile. The 95% CIs for these are based on the Clopper-Pearson method.

Diamond represents the mean and circle represents values outside of 1.5*IQR.

Lower and upper whiskers extend to the most extreme points within 1.5*IQR of Q1 and Q3 respectively.

Probability of new grade 1 or worse liver/pancreatic enzyme abnormalities

Figure 13. Probability of new grade 1 or worse liver / pancreatic enzyme abnormalities



Model is log(p/(1-p)) = intercept + log time-normalized popPK predicted PK parameter, where p is the probability of AE.

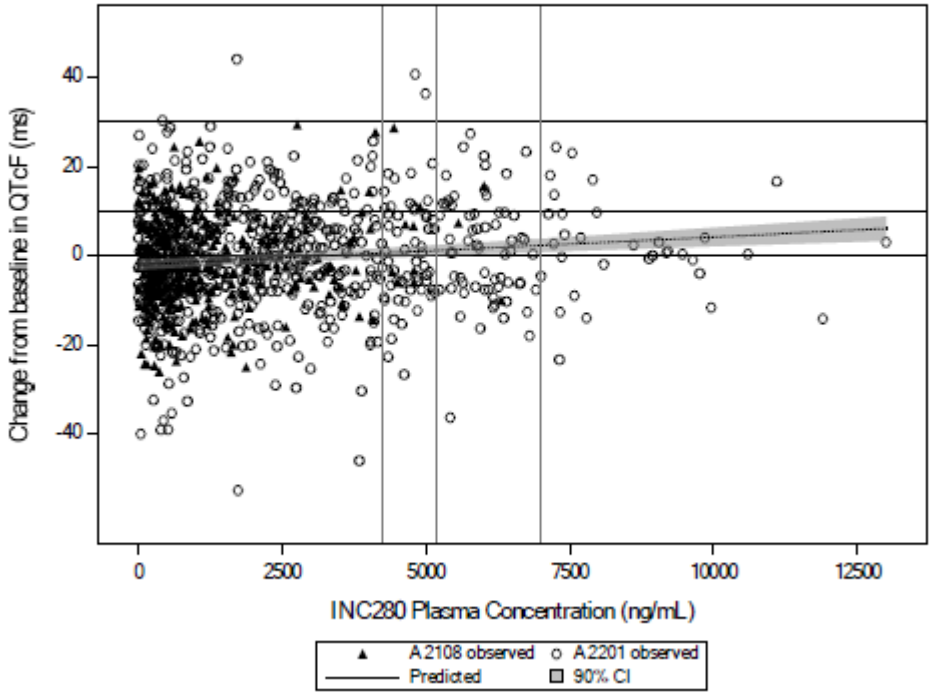
Boundaries are the 95% CI of the logistic regression model estimation.

Secondary pharmacology

Table 23. Estimated model parameters on capmatinib concentration vs. QTcF change from baseline – A2201 and A2108 (PK-ECG set)

Model parameter	Estimate (95% CI)	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	72.297 (45.635, 98.958)	13.534	236.82	5.34	<0.001
Baseline QTcF (ms)	-0.182 (-0.247, -0.117)	0.033	236.22	-5.51	<0.001
INC280 Plasma concentrations (1000 x ng/mL)	0.623 (0.303, 0.936)	0.145	917.31	4.29	<0.001
Baseline is defined as the last non-missing value prior to the first dose. Model is a linear mixed effects model of QTcF change from baseline, including PK concentration and baseline QTcF as fixed effects and subject as a random effect.					

Figure 14. Scatter plot and 90% CI of QTcF change from baseline versus capmatinib concentration in NSCLC patients – A2201 and A2108 (PK-ECG set)



2.6.2.3. Discussion on clinical pharmacology

Bioequivalence

Bioavailability was demonstrated between 2×150 mg tablets (test 1 batch) and 3×100 mg capmatinib in study **X2109**.

The 2×150 mg tablets were not compared to the 1×100 mg + 1×200 mg capmatinib. As the quality characteristics of the to be marketed formulation are very similar between the 150 mg and 200mg tablet and bioequivalence has been shown between 3x 100 mg tablets and the 2x 150 mg FMI, there is no reason to request an additional bioequivalence study to compare 2×150 mg tablets to 1×100 mg + 1×200 mg capmatinib.

Food effects

Food does not alter capmatinib bioavailability to a clinically meaningful extent. Tabrecta can be administered with or without food

Dose proportionality

The dose proportionality analysis suggested a linear relationship in the range between 200 and 600 mg in healthy volunteers.

Time-dependency

The lack of the time-dependency effect on capmatinib exposure was justified.

Pharmacokinetics in the target population

A population pharmacokinetic model was developed using data of studies X1101, X2102, A2108 and A2201, which were conducted in patients with advanced solid tumours, MET dysregulated advanced solid tumours and EGFR wild-type advanced non-small cell lung cancer. A limitation of solely including patient

studies in the population pharmacokinetic model is that no quantitative comparison with healthy volunteers (HV) can be made. Therefore, it is unclear how the results of the healthy volunteer studies can be translated to the intended patient population. Due to the unbalanced distribution of the dataset, the vast majority of the experimental evidence was collected after the administration of 400 and 600 mg bid tablets in fasted individuals. However, it should be pointed out that scarce but relevant experimental evidence was also collected in fed conditions, after qd regimens and capsule formulation at additional dose levels.

The base population PK model incorporates several parameters to describe the variable absorption of capmatinib. In fact, a delayed (ALAG1) zero-order absorption processes modelled as the duration of the zero-order process (D1) was used. The disposition of capmatinib was described using a two compartment model, parametrized in terms of CL, V1, Q and V2. Food and formulation effects were incorporated on ALAG1, D1 and relative bioavailability (F1). According to the VPC provided in Figure 4 and Figure 5, the absorption process is poorly characterized. In general, Cmax is under-predicted by the model and the tmax is anticipated by the model in patients receiving 400 mg tablet. In addition, inter-individual random effects on D1 and ALAG1 were quite large (93 and 151%, respectively), which may suggest that the structural part of the population PK model is not able to address the processes involved in the absorption of capmatinib.

Several absorption models were evaluated, including sequential and parallel 0/0, 1/0, 0/1st, 1st /1st order and also first order with a transit compartment in order to improve the description of the absorption phase. In that sense, the updated model including a sequential 1st/1st order absorption model was compared versus the original model (zero-order model). The model performance of both absorption mechanisms showed adequate characterization of the time-course of capmatinib and no significant improvements were identified when a sequential 1st/1st absorption model was proposed.

Furthermore, the role of the peripheral compartment is quite uncertain, since adequate RSE (<20%) were reported for Q, V2 and their corresponding inter-individual variances, but both inter-individual variances of Q and V2 are extremely large (165 and 497%, respectively). According to the eta-distribution for the categorical covariates, there is a difference between asian and non-asian patients and between japanese and non-japanese patients when capsule formulation was administered. The difference on Q and V2 for the capsule formulation has not been explained by the applicant and, therefore, it should be highlighted that the current population PK model cannot be used for dose selection of the capsule formulation in any sub-group of populations. .

Inter-individual variability was: CL (50%), V_1 (45%), lag-time (ALAG1: 150%), duration of zero-order absorption (D1, 103%), inter-compartmental clearance (Q, 166%) and V_2 (498%). Intra-individual variability was estimated using a combined error model (proportionally 15.2% and additive SD: ±31.6 ng/mL). This indicates that mainly the absorption part of the pharmacokinetic profile is responsible for the large variability, but also the terminal part of the elimination phase is variable. The latter is most likely explained by the limited number of samples collected between 8-24 hours after dosing.

Special populations

A model-based approach using a forest-plot analysis was conducted in order to assess the impact of impaired renal function, impaired hepatic function, gender, race, body weight and age over the exposure metrics (AUC, C_{max} and C_{trough}). No dose adjustment is necessary in patients 65 years of age or older. Population pharmacokinetic analysis showed that there is no clinically relevant effect of age, gender, race, or body weight on the systemic exposure of capmatinib.

Caution should be exercised in patients with severe renal impairment as Tabrecta has not been studied in these patients. No dose adjustment is necessary in patients with mild or moderate renal impairment.

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (see sections 4.2 and 5.2 of the SmPC).

PBPK model validation

Overall, the PBPK report was clear and comprehensive and the model performance appropriate. However, it should be noted that model corrections for CYP3A4 abundance were made but not for other CYPs.

PBPK model evaluation of capmatinib as victim

The interaction with moderate CYP3A inducer efavirenz and moderate CYP3A inhibitors, erythromycin or fluconazole, on capmatinib was simulated.

The model appears to be appropriate for interpolation and rough estimation of the interaction of moderate inhibitors and inducers of CYP3A as the dose titration steps of 400mg/300mg/200mg result in wide clinical exposure range.

PBPK model evaluation of capmatinib as perpetrator

The effect of capmatinib on the metabolism of the CYP2C8 substrate repaglinide, CYP2C9 substrate warfarin, CYP2C19 substrate omeprazole and CYP2B6 substrate buproprion was simulated.

PBPK modelling is used to waive drug-drug interaction studies for the effect of capmatinib on CYP2C9, CYP2C19, CYP2C8 and CYP2B6, therefore, the in vitro data should be robust. Since the potential effects of capmatinib on CYP2C9, CYP2C19 and CYP2C8 are reversible inhibitions and all these inhibition parameters have been determined in HLM, the inhibition constants of the various CYP enzymes can be compared.

Interactions

The applicant evaluated the drug-drug interaction (DDI) risk using in vitro methods, PBPK modelling and clinical DDI studies. These studies and methods generally comply with EMA Guideline on the investigation of drug interactions CPMP/EWP/560/95/Rev. 1 Corr. 2**

Effects of other medicinal products on Capmatinib

Capmatinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. Clinically relevant drug drug interactions between capmatinib and gastric acid reducing agents are unlikely to occur as co administration of rabeprazole (study **A2101**) had no clinically meaningful effect on exposure of capmatinib.

Capmatinib undergoes metabolism through CYP3A4 enzyme and aldehyde oxidase. The risk of a drug drug interaction via aldehyde oxidase has not been evaluated as there are no confirmed clinically relevant inhibitors (see section 4.5 of the SmPC).

Clinical DDI study **A2102** investigated the effect of a strong CYP3A inhibitor (Itraconazole) and a strong CYP3A inducer (rifampicin) on the PK of a single dose of capmatinib in healthy subjects. Based on this study outcome, patients should be closely monitored for adverse reactions during co administration of Tabrecta with strong CYP3A inhibitors, including but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole.

Decreases in capmatinib exposure may decrease Tabrecta anti-tumour activity. Co administration of Tabrecta with strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort (Hypericum perforatum), should be avoided. An alternative medicinal product with no or minimal potential to induce CYP3A should be considered. Caution should be

exercised during co administration of Tabrecta with moderate CYP3A inducers (see section 4.5 of the SmPC).

Based on in vitro data, capmatinib is a Pgp substrate, but not a BCRP or MRP2 substrate. Capmatinib is not a substrate of transporters involved in active hepatic uptake in primary human hepatocytes.

As capmatinib is classified as BCS class 2 drug with a high passive permeability and an estimated bioavailability of 75-100% for the tablet, the effect of Pgp inhibition is expected to be small. Capmatinib could not be identified as a substrate of any active transport processes in primary cultured human hepatocytes.

The effects of capmatinib on other drugs:

In vitro studies showed that capmatinib is an inhibitor of CYP2C8, CYP2C9 and CYP2C19. Capmatinib also showed weak induction of CYP2B6 and CYP2C9 in cultured human hepatocytes. Simulations using PBPK models predicted that capmatinib given at a dose of 400 mg twice daily is unlikely to cause clinically relevant interaction via CYP2B6, CYP2C8, CYP2C9 or CYP2C19.

CMN288 showed little inhibitory potency against CYP2C8, CYP2C9, CYP3A4, but not at clinically relevant concentrations.

Moderate inhibition of CYP1A2 was observed when capmatinib treatment at 400 mg b.i.d. (Study **A2103**) was co-administered with the sensitive CYP1A2 substrate caffeine. If capmatinib is co-administered with narrow therapeutic index CYP1A2 substrates, such as theophylline and tizanidine, dose reduction of the co administered medicinal product may be required.

Clinically relevant drug drug interactions between capmatinib and CYP3A substrates are unlikely to occur as co administration of capmatinib had no clinically meaningful effect on exposure of midazolam (a CYP3A substrate).

The model simulations predict weak inhibition of the metabolism of the CYP2C8 substrate repaglinide, and no clinically relevant effect on the metabolism of the CYP2C9, CYP2C19 and CYP2B6 substrates. According to the applicant, the only known CYP2C8 substrate with narrow therapeutic index so far is paclitaxel, which is unlikely to be given concomitantly with capmatinib.

Based on *in vitro* data, capmatinib and its major metabolite CMN288 showed reversible inhibition of renal transporters MATE1 and MATE2K. Capmatinib may inhibit MATE1 and MATE2K at clinically relevant concentrations.

Based on *in vitro* data, capmatinib showed reversible inhibition of hepatic uptake transporters OATP1B1, OATP1B3, and OCT1. However, capmatinib is not expected to cause clinically relevant inhibition of OATP1B1, OATP1B3, and OCT1 uptake transporters based on the concentration achieved at the therapeutic dose. Capmatinib is not an inhibitor of renal transporters OAT1 or OAT3. Capmatinib is not a MRP2 inhibitor *in vitro*.

Study **A2105** investigated the co-administration of digoxin (P gp substrate) and rosuvastatin (BCRP substrate) with capmatinib indicating that capmatinib can be considered as an inhibitor of P-gp and an inhibitor of BCRP. Co-administration of Tabrecta with a P-gp or BCRP substrate may increase the incidence and severity of adverse reactions of these substrates. Caution should be exercised during co administration of Tabrecta with P gp (digoxin, dabigatran etexilate, colchicine, sitagliptin, saxagliptin and posaconazole) or BCRP (methotrexate, rosuvastatin, pravastatin, mitoxantrone and sulphasalazine) substrates. If capmatinib is co administered with narrow therapeutic index P-gp or BCRP substrates, dose reduction of the co administered medicinal product may be required (see section 4.5 of the SmPC).

In vitro data indicate a low potential of inhibition of hepatic uptake transporter OATP1B1 and OATP1B3. However, in DDI study **A2105** a considerable interaction with probe substrate rosuvastatin (substrate for BCRP and OATP) was observed (3-fold increase of rosuvastatin C_{max}). Therefore, some contribution of inhibition of OATP cannot be excluded.

In **A2102** itraconazole/rifampicin DDI study), the time course of serum creatinine and cystatin C was investigated following single dose of capmatinib. The results indirectly suggest that the transient increase of serum creatinine level may result from reversible inhibition of active renal transporters, in this case, likely MATE1 and MATE2K.

Exposure relevant for safety evaluation

The applicant has provided a model-derived exposure of capmatinib 400 mg tablet according to the different sub-groups of patient's characteristics.

Secondary pharmacology: QTc prolongation

Exposure-QTc relationship was investigated with pooled data from Studies A2201 and A2108. The 75th percentile of Cmax suggested a median change from baseline of 2.30 ms. Therefore, no clinically relevant changes in QTc prolongation are expected after the administration of 400 mg bid of capmatinib.

Exposure-efficacy

The relationship between exposure and efficacy has been evaluated using pop PK-PD methods and efficacy data of patients included in Study A2201 (see methods). With the target dose of 400 mg b.i.d. a 67.9% ORR was achieved in subjects with MET mutated NSCLC, in the first line setting (cohort 5b), while it was 40.6% in the pretreated setting (cohort 4). Exposure-efficacy analyses were conducted using data of patients (n = 94) included in Cohort 4 (2L/3L MET mutated NSCLC) and cohort 5b (1L MET mutated NSCLC) from study A2201.

The exposure-efficacy analysis did not identify any significant relationship between capmatinib and efficacy endpoints. Cavg and Cmax exposure metrics were related to BOR, DOR, and changes in tumour size in MET mutated NSCLC subjects. The Cox regression analysis between Cmax and Cavg on PFS suggested a lower hazard for PFS event with increasing exposure to capmatinib, which is expected. The lack of significant exposure-efficacy relationships could be partially explained by the lack of inclusion of higher dose levels in a pooled analysis (similarly to the exposure-safety analysis) that could expand the exposure range of capmatinib. The expand of the exposure range used in the exposure response analyses is not possible with the experimental data available. Since the current purpose of the presented exposure-efficacy models is descriptive, this limitation is considered acceptable.

Exposure-safety

Exposure-safety analyses were conducted using data of patients (n = 544) included in studies A2201, A2108, X1101, X2102. Subsets were made for different safety outcomes.

The popPK predicted C_{max} and C_{avg} were used as exposure metrics. The safety endpoints selected for exposure-safety analysis were most frequent adverse events (peripheral oedema, nausea/vomiting) or

adverse events of special interest, which had sufficient incidences to conduct the analysis (ALT, AST, TBILI, amylase, lipase).Regarding the exposure-safety analysis, a pooled analysis increased the dataset using a wide range of dose levels. Several endpoints (peripheral edema, nause/vomiting, and liver and pancreatic enzymatic abnormalities) were assessed. A positive relationship was statistically identified between capmatinib exposure and risk of nausea/vomiting events, and of pancreatic enzyme abnormalities. A similar trend was observed when C_{max} or C_{avg} were considered, suggesting a probability between ~20-30% in the range of exposure of capmatinib after 400 mg bid. On the other hand, probability of nausea/vomiting events was predicted in the range of 40-65% in the range of exposure of capmatinib after 400 mg bid. Nonetheless, the statistical method used only provides a rough estimation of the relationship between exposure and response, particularly because the pharmacokinetics are very variable (also anticipated to be high within-individuals), which is not reflected in the exposure-response analyses. Therefore, these analyses should be interpreted with caution.

Dose selection

The dose selection was supported by the population pharmacokinetic analysis, pre-clinical PK/PD relationship, a clinical dose-finding study (X2102) and exposure-response analyses of study A2201. Despite this seemingly, large body of evidence, several uncertainties have been identified with respect to the dose selection. These pertain to:

- **Population pharmacokinetic analysis:** the population pharmacokinetic analysis was used to demonstrate that trough concentrations of capmatinib were above the pre-clinically determined target concentrations. The target concentrations were based on IC90 and IC95 (108 nM [44 ng/mL] and 320 nM [132 ng/mL], respectively), and were derived from PK/PD modelling in mouse S114 allograft model. More than 98% of patients were predicted to reach IC90 at 200 mg, 300 mg, and 400 mg BID. About 82%, 93%, and 96% of patients on 200 mg, 300 mg, and 400 mg BID, respectively, will reach IC95. However, it is questioned whether the mouse model is representative for the clinical situation due to differences in cell types, tumour blood flow, oxygenation, etc. Furthermore, a high number of patients were estimated to be above this target concentration even at the lower dosages, which would suggest that the dose is too high for a large number of patients.
- **Dose finding study X2102:** the selected recommended phase 2 dose (RP2D) is understood from a safety perspective, since the MTD was not reached, and the posterior probability of excessive toxicity was 20.1% for 600 mg bid capsules dose level in the dose escalation phase (i.e. <25% chance that the true DLT rate was greater than or equal to 33%). However, from an efficacy perspective, data may be limited to assure that the RP2D is also the optimal biologically effective dose for the following reasons:
    - The applicant states that the observed steady state C_{trough} concentrations at 600 mg b.i.d capsules was well above the observed C_{trough} concentrations from 3 PR lung cancer patients in study X2102 .
    - Near-complete inhibition was seen at 400-450 mg b.i.d capsule dose levels, which is a lower dose than 600 mg b.i.d capsule (of note: the 600 mg capsule formulation is deemed equivalent to the 400 mg tablet formulation due to increased bioavailability with the tablet formulation, but these results should be interpreted with caution due to this high formulation effect).
    - Clinical activity was observed at the dose levels of 400 mg tablet b.i.d. or 600 mg capsule b.i.d. in patients with MET-dysregulated NSCLC, while the applicant mentions that activity was not evident at lower dose levels. However, the dose-escalation cohorts included various tumour types and employed broad criteria for MET dysregulation, which makes it not surprising these patients did not respond to the lower doses, in retrospect. Especially

considering that patients NSCLC patients with high MET-amplifications (GCN≥10) have the highest chance of a response.

- **Exposure-response analyses (study A2201)**: No relationship between exposure and efficacy outcomes has been quantified, presumably due to the limited number of patients included in the exposure-response analysis for efficacy, the heterogeneous patient population and the relatively simple methodology used. Efficacy endpoints included BOR, DOR, DFS, and best percent change from baseline of tumour size. The exposure response analyses for safety outcomes demonstrates that a lower plasma exposure is accompanied with less side effects such as peripheral oedema. If maximum efficacy is already reached with a lower dose, than a potentially improved tolerability could be achieved.

The applicant provided an efficacy comparison between the patients who received a dose reduction (down to 200 mg twice daily) compared to those who did not receive a dose reduction. The data do not show a detriment for those whose dose was reduced. However, the data must be interpreted with caution, as the two patient populations were not randomised next to that these data cannot be used to substantiate the minimum of the 200 mg dose in case dose reduction is needed.

The dose exposure and dose effect response for doses below 200 mg have not been evaluated. Therefore, it is not known if the product can be effective for doses < 200 mg, for those who cannot tolerate the 300 or 400 mg dose.

2.6.2.4. Conclusions on clinical pharmacology

Bioanalytical analysis for quantification of INC280 and its metabolite CMN288 in support of capmatinib clinical studies were conducted at two different sites; WuXi AppTec Co., Ltd. (Shanghai, China) and XenoBiotic Laboratories, Inc (Wuxi Apptec in New Jersey, USA). The methods are well documented and were cross-validated and overall acceptable.

Pharmacokinetics

Pharmacokinetics of capmatinib have been characterized through non-compartmental and compartmental analyses, evaluating the main aspects in terms of clinical pharmacology. It is agreed that, generally, the pharmacokinetics of capmatinib have been characterised appropriately. The SmPC reflects the pharmacokinetics and the DDI risks appropriately. The results of the studies with the capsule formulation should be interpreted with caution due to a large formulation effect.

Pharmacodynamics

The analysis of exposure-response of capmatinib in patients with MET mutated NSCLC cancer has been performed over several efficacy and safety endpoints by using Cmax and Cavg exposure metrics. The results suggested weak relationship between exposure metrics and efficacy endpoints. Regarding the safety endpoints, a positive trend has been identified between capmatinib exposure and nausea/vomiting events and pancreatic enzyme abnormalities, see clinical safety section.

No dose response -response evaluations have been conducted for doses below 200 mg for the METmut population. Therefore, an uncertainty remains, if the dose can be reduced below the 200 mg, if the higher doses are not tolerated well.

The SmPC indicates that the efficacy of tabrecta in doses < 200 mg has not been investigated in clinical trials.

2.6.3. Clinical efficacy

Main efficacy results supporting the claimed indication come from study CINC280A2201 (also called GEOMETRY mono-1) which is a phase 2, non-randomised, open label study that includes 9 cohorts of patients with NSCLC, which are defined by the type of MET dysregulation (degree of MET amplification vs. MET mutation) and previous treatment status (naïve vs. pre-treated in 2nd/3rd line).

In summary, the evidence supporting the efficacy of capmatinib is limited to non-comparative antitumoral results in a total of 160 (60 naïve + 100 pre-treated) METmut NSCLC subjects. Supportive evidence is limited to some retrospective data aimed to provide contextualisation to the main study results.

Table 24. Overview of key prospective clinical studies and their status

Study no Status/data cut-off date	Study objectives	No of subjects	Capmatinib dose
Studies in subjects with cancer			
Registration study for efficacy and safety			
CINC280A2201 enrollment completed, Study Ongoing 18-Sep-2020	To evaluate antitumor activity of capmatinib in MET-dysregulated advanced NSCLC	373# including 160 MET-mutant subjects : Cohort 4 = 69 Cohort 5b = 28 Cohort 6 = 31 Cohort 7 = 32	400 mg (b.i.d. dosing-tablet)
Phase I study with efficacy and safety data			
CINC280X2102 Completed	Dose escalation: MTD Dose expansion: anti-tumor activity, safety and tolerability	131 (including dose escalation + expansion groups)	Dose escalation 100, 200, 250, 350, 450 mg (b.i.d. dosing-capsule); (n = 25) 600 mg (b.i.d. dosing-capsule): (n = 8) 400 mg (b.i.d. dosing-tablet); (n = 5) Dose expansion 400 mg (b.i.d. dosing-tablet); (n = 93; of which 55 were with NSCLC)

#A2201: N=373 subjects. Cohort 1 (n=69), Cohort 1b (n=42), Cohort 2 (n=54), Cohort 3 (n=30), Cohort 4 (n=69), Cohort 5a (n=15), Cohort 5b (n=28), Cohort 6 (n=34 including 31 MET mutation regardless of MET GCN, 3 with MET GCN≥ 10 without METmut), Cohort 7 (n=32).

2.6.3.1. Dose response study

Study X2102 was an open-label, Phase I single-arm dose-escalation/expansion study, in subjects with MET-dependent advanced solid tumours with two expansion parts:

1. In the original expansion part, subjects with hepatocellular carcinoma (HCC), gastric cancer, NSCLC, and other solid tumours (papillary renal cell carcinoma (pRCC), glioblastoma, and others) were enrolled. MET status was determined using either a local or central laboratory and was based on heterogeneous criteria including a MET H-score ≥ 150 or a ratio of c- MET/centromere ≥ 2.0 or MET gene copy number ≥ 5, or ≥ 50% of tumour cells with immunohistochemistry (IHC) score = 2+ or score = 3+
2. In the second expansion part, subjects with EGFR wt NSCLC harbouring high MET expression (IHC 3+) as determined by central laboratory were enrolled

Four subjects treated with capmatinib in the expansion parts were retrospectively identified with MET-mutated NSCLC. Supportive efficacy data with response assessments per BIRC from these 4 subjects with MET mutated NSCLC are presented in this report as summarized below (Table 25):

Table 25. Summary of Study X2102

Study population pertinent for this SCE report	Subjects with MET-mutated NSCLC
Endpoints	Overall response per subject for subjects with MET-mutated NSCLC, per BIRC by RECIST 1.1
No of subjects enrolled	Four subjects were identified with MET-mutated NSCLC by retrospective central NGS analysis (out of 31 NSCLC with available tumour samples)
Regimen	Capmatinib was administered orally beginning on Cycle 1 Day 1. Each cycle consisted of 28 days.
Treatment duration	Until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason
Tumour assessment	Tumour response (Overall response) by BIRC based on RECIST 1.1. Tumour assessments were performed every 8 weeks.
Statistical methodology	No statistical testing was performed for the efficacy data for the 4 MET mutated NSCLC subjects. Subject listings for efficacy assessments are provided in Study X2102 CSR Addendum 1

- Study results

MET-mutated NSCLC: All 4 subjects with MET-mutated NSCLC were over 65 years of age. Two of them were male and two were female. Three of these subjects had stage IV disease and one had stage Ib disease at initial diagnosis. All 4 subjects had both target and non-target lesions. Tumours were moderately differentiated in one subject with adenocarcinoma, poorly differentiated in another subject with squamous cell carcinoma, and unknown in 2 subjects with large cell carcinoma and unknown histology.

The primary reason for the end of treatment was disease progression for 2 subjects, withdrawal of consent in 1 subject, and loss to follow-up in the fourth subject. One subject was followed for survival.

All 4 subjects showed tumour reductions per BIRC including one confirmed CR, two confirmed PRs, and SD per RECIST 1.1. Per BIRC assessment, the DOR was 16.8+ months for the subject with CR, and 2.1 months and 2.0 months, respectively, for the 2 subjects with PR. The PFS was 18.6+ months for the subject with CR, 3.8 months and 3.9 months for the 2 subjects with PR, and 3.0 months for the subject with SD. These 4 subjects were the first MET mutated NSCLC subjects to be treated with capmatinib and represented the first evidence of activity in this subset of NSCLC.

- *Rationale for the dose selection*

The dose of capmatinib selected to treat subjects with MET-mutated NSCLC in Study A2201 was 400 mg b.i.d. in the tablet formulation.

The MTD/RP2D was to be determined based on the BLRM model assessing the probability of DLTs in the dose escalation phase in separate cohorts of subjects receiving increasing doses of capmatinib and the clinical assessment of safety and PK data including all data up to the end of dose escalation phase. Six dose levels of capmatinib capsules (100 mg bid, 200 mg bid, 250 mg bid, 350 mg bid, 450 mg bid, and 600 mg bid) were investigated in the dose escalation phase.

- Based on the BLRM used to guide dose-escalation, the posterior probability of excessive toxicity was 20.1% for 600 mg bid dose level in the dose escalation phase (i.e. <25% chance that the true DLT rate was greater than or equal to 33%).
- Safety: No DLTs were observed at the 600 mg bid capsule dose level.
- PK: Capmatinib exposure was found to increase by dose up to 600 mg bid dose level and the observed steady state Ctrough concentrations at 600 mg bid was well above the observed Ctrough concentrations from 3 PR lung cancer subjects in Study CINC280X2202.
- Preliminary clinical efficacy: Tumour shrinkage was observed for 2 subjects (colon cancer and HCC) treated with 450 mg bid (capsule) dose level. The efficacy data was not available for the 600 mg bid dose level at the time of RP2D determination. In Study CINC280X2202, 3 PRs were observed in combination with gefitinib in NSCLC (capmatinib steady state Ctrough concentration was 57-216 ng/mL).
- Near-complete PD effect (defined as p-MET inhibition) was observed in a subject with colorectal cancer at 450 mg bid capsule dose level.

Based on the considerations of the estimated MTD by the BLRM model along with overall assessment of safety, PK and PD results, and preliminary clinical efficacy data, the RP2D was determined to be 600 mg bid in capsule formulation. However, the number of capsules taken by the subjects was a limiting factor as 12 capsules had to be taken twice daily at the 600 mg bid dose regimen.

A tablet formulation was developed to support commercialization and subsequently introduced into Study X2102 at the 400 mg b.i.d. dose level. An evaluation of the relative bioavailability indicated that the capmatinib tablet at 400 mg b.i.d. provided comparable geometric mean AUC0-12h, ss (0.98-fold) and slightly higher Cmax, ss (1.20-fold) compared with the capmatinib capsule at 600 mg b.i.d. These data provided rationale for the selection of 400 mg b.i.d. as the tablet RP2D. Both the 600 mg capsule b.i.d. and 400 mg tablet b.i.d. demonstrated comparable safety profiles and were well tolerated.

The rationale for the capmatinib 400 mg tablet b.i.d. dose and schedule is based on the totality of evidence available from both capsule and tablet formulations including clinical efficacy, safety, pharmacokinetic and pharmacodynamic data, as summarized below:

- Clinical activity was observed at the dose levels of 400 mg tablet b.i.d. or 600 mg capsule b.i.d. in the dose finding Study X2102 in subjects with MET-dysregulated NSCLC and was not evident at lower dose levels: 13 out of 55 (23.6%) subjects in the expansion phase had a CR or PR. Three out of 4 subjects in this study harbouring MET mutation achieved a confirmed CR or PR. Eight out of 15 (53.3%) NSCLC subjects with MET amplification (GCN ≥ 6) had a CR or PR. Furthermore, in Study A2201, capmatinib 400 mg tablet b.i.d. demonstrated efficacy in subjects with NSCLC harbouring MET exon 14 mutation in the treatment-naïve and pretreated settings (ORR per BIRC was 67.9% (95% CI: 47.6, 84.1) and 65.6% (95% CI: 46.8, 81.4) in Cohorts 5b and 7, respectively, and was 40.6% (95% CI: 28.9, 53.1) and 51.6% (95% CI: 33.1, 69.8) in Cohorts 4 and 6, respectively) (Section 2.1).
- The observed safety profiles of capmatinib 400 mg tablet b.i.d. and 600 mg capsule b.i.d. were consistent, well tolerated, manageable and predictable in the intended patient population, with the majority of treatment-related AEs grade 1/2 in severity [Study A2201 DCO 18-Sep-2020-Table

14.3.1-1.4]. Further, safety data from Study A2201 showed an acceptable safety profile of capmatinib 400 mg tablet b.i.d. and it remained consistent with the observed safety profile in Study X2102.

- A high degree of target inhibition is expected to be maintained during the dosing interval in the majority of patients treated with capmatinib 400 mg tablet b.i.d. Population PK analysis indicated that for the 400 mg tablet b.i.d. regimen, 96% of subjects are expected to have steady state capmatinib unbound plasma trough concentrations above the IC95 for MET inhibition associated with anti-tumour activity in the S114 mouse allograft model. Clinical pharmacodynamic data from tumour biopsies, although sparse, appear consistent: 1 subject with advanced colorectal cancer had near-complete phosphorylated-MET inhibition at 450 mg capsule b.i.d. and 2 subjects with NSCLC in the expansion phase had phosphorylated-MET inhibition of 95% at RP2D.

In summary, the choice for the chosen dose of capmatinib selected to treat subjects with MET-mutated NSCLC in Study A2201 was 400 mg b.i.d. in the tablet formulation, based on all information available can be understood.

2.6.3.2. Main study

CINC280A2201 (A2201): A Phase II, multicenter study of oral MET inhibitor INC280 in adult subjects with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC) -GEOMETRY MONO-1 STUDY

Methods

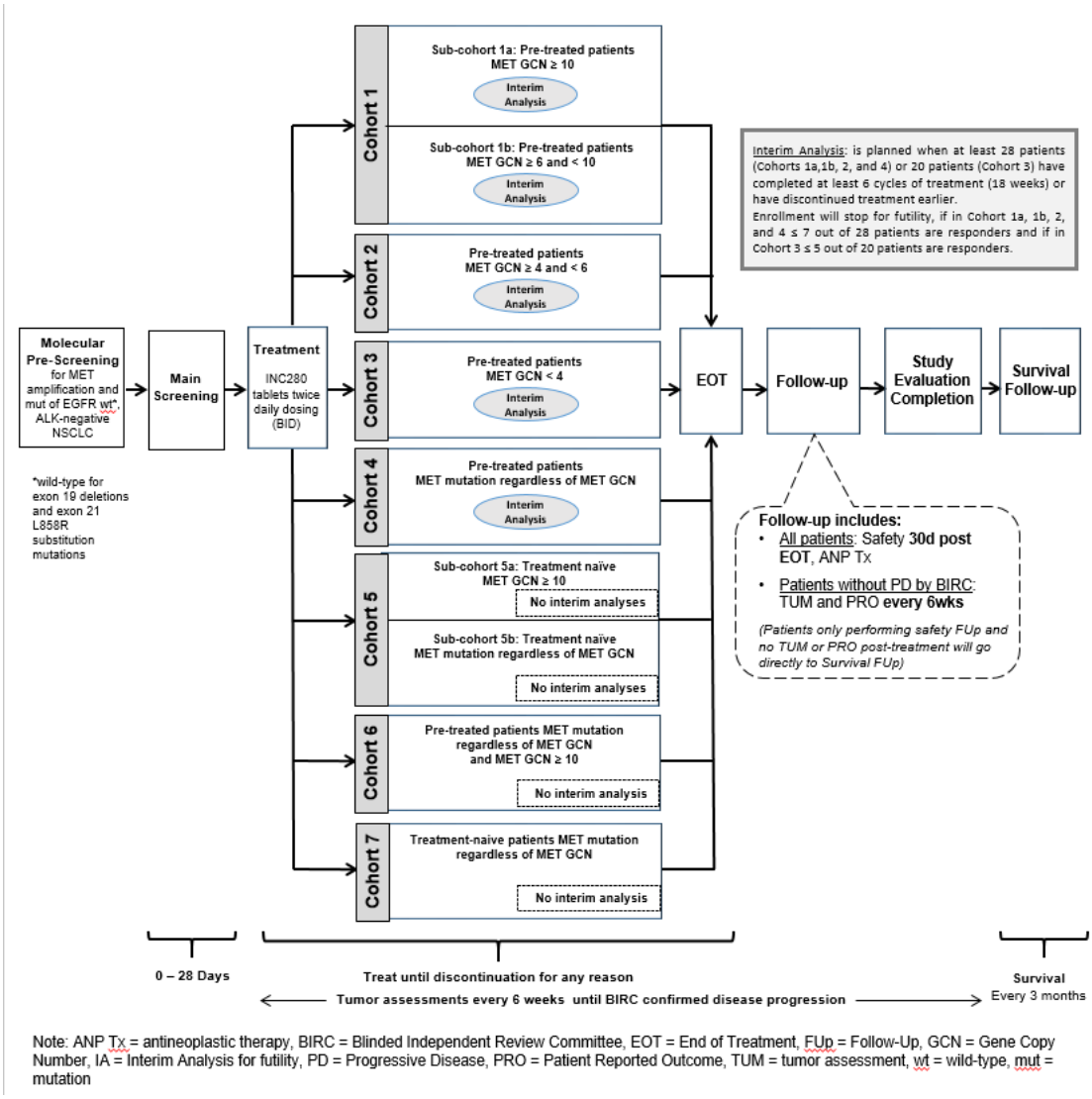
This is a prospectively designed, multicentre, open-label, Phase II study with Bayesian interim monitoring to evaluate the efficacy and safety of single-agent capmatinib in subjects with EGFRwt (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-negative rearrangement, advanced (stage IIIB or IV) NSCLC harbouring MET amplification (detected by FISH) and/or mutations (detected by RT-PCR).

The study has 5 distinct phases: molecular pre-screening, main screening, treatment, post-treatment follow-up (safety and tumour), and survival follow-up (Figure 15).

This study enrolled subjects across 9 distinct cohorts (1a, 1b, 2, 3, 4, 5a, 5b, 6 and 7) according to the to the previous systemic treatment status, MET-amplified NSCLC status, and MET mutation status. Expansion Cohorts 6 and 7 were added to generate additional supportive safety and efficacy data in the pre-treated and treatment-naïve settings, respectively, in consideration of feedback from HA consultations.

Enrolment to all cohorts has been closed (last subject was enrolled on 12-Mar-2020 in Cohort 7)

Figure 15. Study design



Note: ANP Tx = antineoplastic therapy, BIRC = Blinded Independent Review Committee, EOT = End of Treatment, FUp = Follow-Up, GCN = Gene Copy Number, IA = Interim Analysis for futility, PD = Progressive Disease, PRO = Patient Reported Outcome, TUM = tumor assessment, wt = wild-type, mut = mutation

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- **Study Participants**

152 centers across 25 countries participated in the study: Argentina (4 centers), Austria (1 center), Belgium (1 center), Brazil (5 centers), Canada (2 centers), France (11 centers), Germany (16 centers), Israel (4 centers), Italy (18 centers), Japan (11 centers), Korea (5 centers), Lebanon (3 centers), Mexico (2 centers), Netherlands (4 centers), Norway (1 center), Poland (3 centers), Russia (4 centers), Singapore (2 centers), Spain (11 centers), Sweden (2 centers), Switzerland (1 center), Taiwan (5 centers), Turkey (2 centers), UK (4 centers), US (30 centers).

This study enrolled adult male and female subjects with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-negative rearrangement, MET dysregulated, locally advanced or metastatic (stage IIIB or IV) NSCLC, who had failed one or two prior lines of systemic therapy (Cohorts

1a, 1b, 2, 3, and 4), or who had failed one prior line of systemic therapy (Cohort 6), or who had not received any systemic therapy (Cohorts 5a, 5b, and 7) for advanced disease.

Inclusion criteria

Subjects eligible for inclusion in this study were required to meet all of the following criteria:

1. Adult male/female ≥ 18 years at the time of informed consent and who signed informed consent before any screening procedures

2. Subjects with Stage IIIB or IV NSCLC (any histology) at the time of study entry

3. Subjects with histologically or cytologically confirmed diagnosis of NSCLC that is:

    a. EGFR wt status (for exon 19 deletions and exon 21 L858R substitution mutations)

    b. and ALK rearrangement-negative

    c. and MET mutation and/or amplification status.

4. For Cohorts 1a, 1b, 2, 3, 4 subjects must have failed one or two prior lines of systemic therapy for advanced disease (stage IIIB or IV NSCLC). For Cohort 6, subjects must have failed one prior line of systemic therapy for advanced disease (stage IIIB or IV NSCLC). Treatment failure was defined as documented disease progression or intolerance to treatment. Maintenance therapy given after first-line chemotherapy was considered as part of the first line if given to subjects with documented response or stable disease (SD) before starting the maintenance therapy. Neo-adjuvant and adjuvant systemic therapies were counted as one prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.

For Cohorts 5a, 5b, and 7, subjects must not have received any systemic therapy for advanced disease (stage IIIB or IV NSCLC). Neo-adjuvant and adjuvant systemic therapies were not counted as one prior line of treatment if relapse occurred > 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.

5. Subjects with at least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there was clear sign of progression since the irradiation.

6. Subjects who recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (Common Terminology Criteria for Adverse Events [CTCAE] v 4.03). Subjects with any grade of alopecia were allowed to enter the study.

7. Subjects with adequate organ function including the following laboratory values at the screening visit:

- Absolute neutrophil count (ANC) ≥ 1.5 × 109 /L without growth factor support
- Platelets ≥ 75 × 109 /L
- Haemoglobin (Hgb) > 9 g/dL
- Calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 45 mL/min
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
- Aspartate transaminase (AST) ≤ 3 × ULN, except for subjects with liver metastasis,
- who may only be included if AST ≤ 5 × ULN
- Alanine transaminase (ALT) ≤ 3 × ULN, except for subjects with liver metastasis, who
- may only be included if ALT ≤ 5 × ULN

- Alkaline phosphatase (ALP) ≤ 5 × ULN
- Asymptomatic serum amylase grade ≤ 2. Subjects with grade 1 or grade 2 serum
- amylase at the beginning of the study must be confirmed to have no signs and/or
- symptoms suggesting pancreatitis or pancreatic injury (e.g. elevated P-amylase,
- abnormal imaging findings of pancreas, etc)
- Serum lipase ≤ ULN
- Fasting plasma glucose ≤ 175 mg/dL (≤ 9.7 mmol/L)
- Subjects had the following laboratory values within the laboratory normal limits or
- corrected to within normal limits with supplements during screening:
    - Potassium
    - Magnesium
    - Phosphorus
    - Total calcium (corrected for serum albumin)

8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1

9. Subjects who were willing and able to comply with scheduled visits, treatment plan and laboratory tests.

Exclusion criteria

Subjects eligible for this study must not have met any of the following criteria:

1. Prior treatment with crizotinib, or any other MET or HGF inhibitor

2. Known hypersensitivity to any of the excipients of capmatinib (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).

3. Characterized EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 mutations.

4. Characterized ALK-positive rearrangement.

5. Symptomatic central nervous system (CNS) metastases which were neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms.

6. Presence or history of carcinomatous meningitis.

7. Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.

8. Clinically significant, uncontrolled heart diseases including any of the following:

- Unstable angina within 6 months prior to screening
- Myocardial infarction within 6 months prior to screening
- History of documented congestive heart failure (New York Heart Association functional classification III-IV)

- Uncontrolled hypertension defined by a systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) was allowed prior to screening.
- Ventricular arrhythmias
- Supraventricular and nodal arrhythmias not controlled with medication
- Other cardiac arrhythmia not controlled with medication
- QTcF ≥ 450 ms (male subjects), ≥ 460 ms (female subjects) on the screening ECG (as mean of triplicate ECG)

9. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting capmatinib or subjects who had not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤ 2 weeks prior to starting capmatinib or subjects who had not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting capmatinib was allowed.

10. Major surgery (e.g. intra-thoracic, intra-abdominal, or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting capmatinib or who had not recovered from side effects of such a procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy were not considered as major surgery and subjects could be enrolled in the study ≥ 1 week after the procedure.

11. Receiving treatment with strong inducers of CYP3A4 and could not be discontinued ≥ 1 week prior to the start of treatment with capmatinib and for the duration of the study

12. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of capmatinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, or malabsorption syndrome).

13. Unable or unwilling to swallow tablets as per dosing schedule.

14. Receiving unstable or increasing doses of corticosteroids. If subjects were receiving corticosteroids for endocrine deficiencies or tumour-associated symptoms other than CNS related, dose must have been stabilized (or decreasing) for ≥ 5 days before first dose of capmatinib.

15. Receiving treatment with any enzyme-inducing anticonvulsant that could not be discontinued ≥ 1 week before first dose of capmatinib, and for the duration of the study. Subjects receiving non-enzyme-inducing anticonvulsants were eligible.

16. Applicable to Cohorts 1-4 and Cohort 6 only: previous anticancer and investigational agents within 4 weeks or ≤ 5 × half-life of the agent (whichever was longer) before first dose of capmatinib. If previous treatment was a monoclonal antibody, then the treatment must have been discontinued ≥ 4 weeks before first dose of capmatinib. If previous treatment was an oral targeted agent, then the treatment must have been discontinued ≥ 5 × half-life of the agent before the first dose of capmatinib.

17. Other severe, acute, or chronic medical or psychotic conditions or laboratory abnormalities that in the opinion of the Investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results.

18. Any other condition that would, in the Investigator's judgment, contraindicate participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g. infection (including active hepatitis B and C), inflammation, intestinal obstruction, unable to swallow medication, social/psychological issues, etc.

19. Pregnant or nursing (lactating) women.

20. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing and for 7 days after stopping treatment. Highly effective contraceptive methods and guidance on women who were considered postmenopausal and not of childbearing potential are listed in Appendix 16.1.1-Protocol-Section 5.3. In case of use of oral contraception, women should have been stable on the same pill for ≥ 3 months before taking study treatment.

21. Sexually active males unless they used a condom during intercourse while taking drug and for 7 days after stopping treatment and should not father a child in this period. A condom was required to be used also by vasectomized men as well as during intercourse with a male partner to prevent delivery of the drug via semen.

22. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e. affecting activities of daily living or requiring therapeutic intervention).

- **Treatments**

Regimen: Capmatinib tablet was administered orally on a continuous twice daily (b.i.d.) dosing schedule, on a flat scale of mg/day and not individually adjusted by weight or body surface area. A complete cycle of treatment was defined as 21 days of twice daily treatment with capmatinib.

Treatment duration: Until disease progression as determined by the Investigator and confirmed by BIRC, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments were permitted in order to allow the patient to continue the study treatment.

In Cohorts 1a, 1b, 2, 3, 4, 5a, and 5b, capmatinib was administered in fasted state and in Cohorts 6 and 7, capmatinib was administered with or without food.

- **Objectives/endpoints**

Primary and secondary objectives and related endpoints are described below:

Table 26. Study objectives and related endpoints

Objective	Endpoint
Primary objective	
To evaluate the antitumor activity of capmatinib, as measured by overall response rate (ORR) by Blinded Independent Review Committee (BIRC) assessment, by cohort	ORR, proportion of subjects with a best overall response (BOR) defined as complete response or partial response (CR+PR) by BIRC assessment per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
Key secondary objective	
To evaluate duration of response (DOR) as assessed by BIRC, by cohort	DOR, calculated as the time from the date of the first documented CR or PR by BIRC per RECIST 1.1 to the first documented progression or death due to any cause for subjects with PR or CR
Other secondary objectives	
To evaluate ORR and DOR by investigator assessment, by cohort	ORR (CR+PR) and DOR per RECIST 1.1 by investigator assessment
To evaluate time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) by investigator and by BIRC assessment, by cohort	All calculated per RECIST 1.1, both by BIRC and investigator: • TTR, calculated as the time from first dose of capmatinib to first documented response (CR+PR) for subjects with PR or CR • DCR, calculated as the proportion of subjects with BOR of CR, PR, or stable disease (SD) • PFS, defined as time from first dose of capmatinib to progression or death due to any cause
To evaluate overall survival (OS), by cohort	OS, defined as time from first dose of capmatinib to death due to any cause
To evaluate capmatinib safety profile as monotherapy in NSCLC subjects with advanced/metastatic disease	Incidence of adverse events (AEs) and serious adverse events (SAEs), change in vital signs, laboratory results (hematology, blood chemistry, and urinalysis) and electrocardiogram (ECG)
To characterize the PK of capmatinib and metabolite CMN288	Plasma concentration-time profiles and PK parameters estimated by non-compartmental analysis or population PK modeling
Exploratory objectives	
To explore the exposure-response relationship, where responses include efficacy and safety endpoints	Correlation of efficacy and safety endpoints with PK parameters
To explore the exposure-ECG relationship	Correlation of ECG change from baseline with PK parameters
To assess the correlation between amplification and/or mutation status of the MET oncogene	Correlation between amplification and/or mutation status in tumor material collected

To assess correlation of MET amplification as determined by GCN and gene ratio	Correlation between MET amplification by GCN and gene ratio as determined by FISH
To assess correlation of MET amplification determined by gene ratio or GCN and ORR	Correlation between MET amplification as determined by gene ratio or GCN using FISH and ORR
To explore utility of circulating tumor DNA to assess MET amplification and/or mutation status	Correlation between MET amplification and/or mutation status determined in tumor material collected for molecular screening and that determined in circulating tumor DNA collected at baseline
To assess the correlation between MET status by next-generation sequencing (NGS) and amplification and/or mutation status of the MET oncogene	Correlation between MET amplification and/or mutation status determined by FISH/RT-PCR at molecular screening and the MET amplification and/or mutation status determined by NGS
To assess the correlation between MET status by NGS and ORR	Correlation between NGS-determined MET status and ORR
To assess potential mechanisms of resistance to MET therapy	Targeted sequencing of a tumor associated gene panel in archival or newly acquired biopsy and subsequent paired newly acquired biopsy, where available, at end of treatment (EOT) if subject discontinued due to progressive disease (PD) or at first PD if subject continues treatment post progression
To assess health-related quality of life (HRQoL)	Change from screening in European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and LC13 and EuroQoL-5 Dimension-5 Level (EQ-5D-5L) questionnaires

The focus of the efficacy analysis is based on data from treatment-naïve MET-mutated NSCLC subjects enrolled in Cohort 5b (28) supplemented by Cohort 7 (32), and from pre-treated MET-mutated NSCLC subjects enrolled in Cohort 4 (69 in 2nd/ 3rd line) supplemented by Cohort 6 (31 in 2nd line).

- **Sample size**

No inferential analyses were planned for this study as this was formally a non-comparative study of several cohorts of patients exposed to capmatinib. The initially targeted sample size was 69 subjects for Cohorts 1a, 1b, 2, 3, and 4, 27 subjects per cohort in Cohorts 5a and 5b, approximately 30 subjects in Cohort 6 and approximately 27 subjects in Cohort 7, if none of the Cohorts 1-4 was stopped for futility at the time of the interim analysis. The aim was to show an ORR with the lower bound of the 95% confident limit above that considered clinically relevant for the two main clinical settings, i.e. 35% for treatment naïve, and 25% for the pre-treated cohorts. Interim analysis for futility were planned in the study protocol for Cohorts 1a, 1b, 2, 3, and 4, with clearly established stopping criteria (POS <10%).

- **Randomisation and blinding (masking)**

This was a 9-cohort non-randomised, open label clinical trial.

Enrolment in each cohort was controlled via an Interactive Response Technology (IRT) system. Each cohort of the study enrolled subjects in parallel with the exception of Cohorts 6 and 7 which was initiated only upon enrolment completion of the respective Cohorts (C1a or C4 for Cohort 6 and C5b for Cohort C7).

- **Statistical methods**

The primary analysis was performed on the **full analysis set (FAS),** which includes all patients who receive at least one dose of capmatinib.

The **primary efficacy endpoint ORR**, defined as the proportion of patients with a best overall confirmed complete response (CR) or partial response (PR), as assessed per RECIST 1.1 by BIRC, was estimated and the exact 95% CI was provided by cohort.

The primary analysis will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) (Clopper and Pearson 1934) provided by cohort/sub-cohort.

In Cohorts 1-4, treatment with INC280 would be considered to have clinically relevant efficacy in a cohort/sub-cohort if an ORR of ~35% is observed in that cohort for the corresponding primary analysis.

In addition, 5 hypotheses will be tested as following for the cohorts/sub-cohorts respectively (Hi0 and Hi1 correspond to cohort/sub-cohort i where i=1a, 1b, 2, 3 or 4)

Hi0: ORR ≤ 25%

In favour of the alternative

Hi1: ORR > 25%

For Sub-cohorts 5a, 5b and Cohort 7, treatment with INC280 would be considered to have clinically relevant efficacy if an ORR of ~55% is observed in that cohort for the corresponding primary analysis. In addition, 3 hypotheses will be tested as following for the cohorts/sub-cohorts (Hi0 and Hi1 correspond to Sub-cohort i where i=5a, 5b or 7):

Hi0: ORR ≤ 35%

In favour of the alternative

Hi1: ORR > 35%

The primary analysis was conducted when all treated patients in cohorts that are not stopped for futility (at the time of the interim analysis) have completed at least 6 cycles of treatment (18 weeks) unless a patient has discontinued treatment earlier.

The efficacy data for treatment-naïve and pre-treated subjects was analysed independently, i.e. separately per cohort and pooled as treatment-naïve (Cohorts 5b + 7) and pre-treated (Cohorts 4 + 6) to further characterize the data.

The key secondary objective was to evaluate **DOR as assessed by BIRC, by cohort**. Among subjects with a confirmed response (CR or PR), DOR was defined as the time from first documented response (CR or PR) to the date of first documented progressive disease (PD) or death due to any cause. If a subject did not have an event, DOR was censored at the date of last adequate tumour assessment.

Other secondary objectives included DCR, TTR, PFS, and OS, and were all conducted on the FAS.

--**ORR by investigator assessment**, by cohort: The evaluation of ORR will be also conducted based on investigator assessment. ORR will be estimated and the exact binomial 95% CI will be provided by cohort.

--**DOR by investigator assessment**, by cohort: The evaluation of DOR will be conducted based on investigator assessment. DOR will be analysed as described above for the analyses based on BIRC assessment.

Table 27. Outcome and event dates for DOR and PFS analyses

	Situation	Date	Outcome
A	No baseline assessment	Date of first dose of study drug [a]	Censored
B	Progression at or before next scheduled Assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment	Censored
D	No progression	Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A	Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given	Ignore the new anticancer therapy and follow situations above	As per above situations
G	Deaths due to reason other than deterioration of 'Study indication'	Date of death	Progressed

[a] The rare exception to this was if the patient died no later than the time of the second scheduled assessment as defined in the protocol in which case this was a PFS event at the date of death

Table 27 presents the censoring rules for the DOR and PFS analyses. The rule to censor patients at the date of last adequate assessment if progression or death occurs after two or more missed assessments

is potentially informative. While rules E and F follow the treatment policy estimand strategy, given the single-arm nature of the trial, it is important to explore the sensitivity of these results to different assumptions (e.g. treatment discontinuation due to clinical progression or anticancer therapy are events). This is discussed further in the context of the results.

--**Overall survival (OS),** by cohort: OS is defined as the time from the date of first dose of INC280 to the date of death due to any cause. If the patient is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cutoff date. OS will be described in tabular and graphical format, by cohort, using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. Censoring reasons will also be summarized.

-The following secondary efficacy objectives will be assessed separately based on investigator assessment and BIRC assessment per RECIST 1.1:

Time to response (TTR), by cohort: Time to overall response of CR or PR (TTR) is defined as the time from start of study drug to first documented response (CR or PR, which must be confirmed subsequently) for patients with a confirmed CR or PR.

Disease control rate (DCR), by cohort: DCR is defined as the proportion of patients with best overall response of CR, PR, or SD per RECIST 1.1. DCR will be estimated and the binomial exact 95% CI will be provided by cohort/sub-cohort.

Progression-free survival (PFS), by cohort: PFS is defined as the time from the date of first dose of INC280 to the date of first radiologically documented disease progression per RECIST 1.1 or death due to any cause. If a patient has not progressed or is not known to have died at the date of analysis cut-off, PFS will be censored at the date of the last adequate tumour evaluation before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1 documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of the new cancer therapy. Clinical deterioration will not be considered as a qualifying event for progression. PFS will be censored at the last adequate tumour assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumour assessments. PFS will be described in tabular and graphical format, by cohort, using Kaplan- Meier methods, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. Censoring reasons will also be summarized.

Other populations of analysis include:

-The Safety analyses set (Safety Set) is identical to the FAS.

-The primary analyses on FAS will be repeated on the Per-Protocol Set (PPS). The PPS consists of a subset of patients in the FAS who have no major protocol deviations, who have an adequate tumour assessment at baseline and have a follow-up tumour assessment > 5 weeks after starting treatment (unless PD is observed before that time).

Results

- **Participant flow**

Overall, 472 subjects signed the main study informed consent, among whom 373 subjects (79.0%) completed the screening phase and had at least one dose of study treatment. Of the 99 subjects who did not continue into the treatment phase, 86 subjects (18.2%) failed screening assessment, 6 subjects each (1.3%) died or discontinued due to subject/guardian decision, and 1 subject (0.2%) had an AE (Table 28).

Table 28. Patient disposition - screening phase. All screened patients

Disposition/Reason	All Patients N=472 n(%)
Entered screening phase	
Ongoing* in the screening phase	0 (0.0)
Completed screening phase	373 (79.0)
Discontinued prior to screening phase completion	99 (21.0)
Primary reason for not completing screening phase	
Adverse event	1 (0.2)
Death	6 (1.3)
Screen failure	86 (18.2)
Subject/guardian decision	6 (1.3)

Sixty-nine subjects were enrolled in Cohort 1a, 42 in Cohort 1b, 54 in Cohort 2, 30 in Cohort 3, **69 in Cohort 4**, 15 in Cohort 5a, **28 in Cohort 5b**, **34 in Cohort 6 (including 31 with MET mutations**), and **32 in Cohort 7**. The enrolment is closed for all cohorts. Enrolment in Cohorts 1b, 2, and 3 was stopped for futility.

The study is ongoing. Thirty-seven subjects (9.9%) were still on study treatment and 336 subjects (90.1%) had discontinued the study treatment. The most frequently reported primary reason for discontinuation from the study was disease progression (230 subjects; 61.7%). Sixty-one subjects (16.4%) discontinued from the treatment phase due to AEs.

Cohort 4 (MET mutated, pre-treated)

In Cohort 4, 69 subjects were enrolled, and 4 subjects (5.8%) are ongoing in the treatment phase, with a median follow-up of 39.7 months (range: 29.5 to 53.3). Disease progression was the primary reason for the end of treatment in 62.3% of subjects. No subject is ongoing in the post treatment follow-up phase.

Cohort 6 (MET mutated, pre-treated)

In Cohort 6, 31 MET mutated subjects were enrolled (in addition to 3 subjects with MET amplification not included in this analysis) and 10 subjects (32.3%) are ongoing in the treatment phase, with a median follow-up of 19.5 months (range: 15.7 to 26.7). Disease progression was the primary reason for the end of treatment in 48.4% of subjects. One subject (3.2%) is ongoing in the post-treatment follow-up phase.

All subjects MET mutated, pre-treated (Cohort 4 + Cohort 6)

One-hundred MET mutated pre-treated subjects were enrolled and 14 subjects (14.0%) are ongoing in the treatment phase, with a median follow-up of 35.1 months (range: 15.7 to 53.3). Disease progression was the primary reason for the end of treatment in 58.0% of subjects. One subject (1.0%) is ongoing in the post-treatment follow-up phase.

Cohort 5b (MET mutated, treatment naïve)

In Cohort 5b, 28 subjects were enrolled with 4 subjects (14.3%) ongoing in the treatment phase, with a median follow-up of 34.0 months (range: 27.5 to 42.0). Disease progression was the primary reason for the end of treatment in 50.0% of subjects. No subject is ongoing in the post treatment follow-up phase.

Cohort 7 (MET mutated, treatment naïve)

In Cohort 7, 32 subjects were enrolled with 15 subjects (46.9%) ongoing in the treatment phase, with a median follow-up of 10.0 months (range: 6.3 to 15.2). Disease progression was the primary reason for the end of treatment in 25.0% of subjects. One subject (3.1%) is ongoing in the post-treatment follow-up phase.

All subjects MET mutated, treatment naïve (Cohort 5b + Cohort 7)

Sixty MET mutated treatment naïve subjects were enrolled in total with 19 subjects (31.7%) ongoing in the treatment phase, with a median follow-up of 14.5 months (range: 6.3 to 42.0). Disease progression was the primary reason for the end of treatment in 36.7% of subjects. One subject (1.7%) is ongoing in the post-treatment follow-up phase.

Table 29. Subject disposition by cohort (Full analysis set)

Disposition/Reason	Cohort 4 (2/3L, Mutant) N=69 n (%)	Cohort 6 (2L, Mutant) N=31 n (%)	All subjects (2/3L, Mutant) N=100 n (%)	Cohort 5b (1L, Mutant) N=28 n (%)	Cohort 7 (1L, Mutant) N=32 n (%)	All subjects (1L, Mutant) N=60 n (%)	All Mutant Subjects (Cohorts 4+6+5b+7) N=160 n (%)	All subjects N=373 n (%)
Treatment Phase								
Ongoing*	4 (5.8)	10 (32.3)	14 (14.0)	4 (14.3)	15 (46.9)	19 (31.7)	33 (20.6)	37 (9.9)
Discontinued from treatment phase	65 (94.2)	21 (67.7)	86 (86.0)	24 (85.7)	17 (53.1)	41 (68.3)	127 (79.4)	336 (90.1)
Entered post-treatment follow-up	22 (31.9)	3 (9.7)	25 (25.0)	6 (21.4)	5 (15.6)	11 (18.3)	36 (22.5)	92 (24.7)
Entered survival follow-up	34 (49.3)	9 (29.0)	43 (43.0)	12 (42.9)	9 (28.1)	21 (35.0)	64 (40.0)	196 (52.5)
Discontinued from study	9 (13.0)	9 (29.0)	18 (18.0)	6 (21.4)	3 (9.4)	9 (15.0)	27 (16.9)	48 (12.9)
Primary reason for discontinuation from treatment phase								
Adverse event	14 (20.3)	4 (12.9)	18 (18.0)	6 (21.4)	4 (12.5)	10 (16.7)	28 (17.5)	61 (16.4)
Death	0	0	0	0	1 (3.1)	1 (1.7)	1 (0.6)	3 (0.8)
Physician decision	4 (5.8)	1 (3.2)	5 (5.0)	2 (7.1)	4 (12.5)	6 (10.0)	11 (6.9)	25 (6.7)
Progressive disease	43 (62.3)	15 (48.4)	58 (58.0)	14 (50.0)	8 (25.0)	22 (36.7)	80 (50.0)	230 (61.7)
Protocol deviation	0	0	0	0	0	0	0	1 (0.3)
Subject/guardian decision	4 (5.8)	1 (3.2)	5 (5.0)	2 (7.1)	0	2 (3.3)	7 (4.4)	16 (4.3)
Post-treatment follow-up								
Ongoing*	0	1 (3.2)	1 (1.0)	0	1 (3.1)	1 (1.7)	2 (1.3)	2 (0.5)
Discontinued from post-treatment follow-up	22 (31.9)	2 (6.5)	24 (24.0)	6 (21.4)	4 (12.5)	10 (16.7)	34 (21.3)	90 (24.1)
Entered survival follow-up after discontinuation from post- treatment follow-up	13 (18.8)	2 (6.5)	15 (15.0)	4 (14.3)	1 (3.1)	5 (8.3)	20 (12.5)	58 (15.5)
Discontinued from study	9 (13.0)	0	9 (9.0)	2 (7.1)	3 (9.4)	5 (8.3)	14 (8.8)	32 (8.6)
Primary reason for discontinuation from post-treatment follow-up								
Adverse event	2 (2.9)	0	2 (2.0)	0	0	0	2 (1.3)	3 (0.8)
Death	0	0	0	0	0	0	0	1 (0.3)
Lost to follow-up	0	0	0	0	0	0	0	1 (0.3)
Physician decision	4 (5.8)	0	4 (4.0)	1 (3.6)	1 (3.1)	2 (3.3)	6 (3.8)	18 (4.8)
Progressive disease	15 (21.7)	2 (6.5)	17 (17.0)	5 (17.9)	2 (6.3)	7 (11.7)	24 (15.0)	54 (14.5)
Subject/guardian decision	1 (1.4)	0	1 (1.0)	0	1 (3.1)	1 (1.7)	2 (1.3)	13 (3.5)

* Subjects ongoing at the time of the cut-off 18-Sep-2020
- Percentage is based on N
- Reasons for discontinuation are from 'End of Treatment Phase Disposition' and 'End of Post Treatment Phase Disposition' CRF pages.

Patient´s disposition for the key cohorts relevant to this application:

-*Pre-treated subjects*: In Cohort 4, 69 subjects were enrolled, and 4 subjects (5.8%) are ongoing in the treatment phase, with a median follow-up of 39.7 months (range: 29.5 to 53.3). Disease progression was the primary reason for the end of treatment in 62.3% of subjects. In Cohort 6, 31 MET mutated subjects were enrolled (in addition to 3 subjects with MET amplification not included in this analysis) and 10 subjects (32.3%) are ongoing in the treatment phase, with a median follow-up of 19.5 months (range: 15.7 to 26.7). Disease progression was the primary reason for the end of treatment in 48.4% of subjects.

- *Treatment Naïve subjects*: In Cohort 5b, 28 subjects were enrolled with 4 subjects (14.3%) ongoing in the treatment phase, with a median follow-up of 34.0 months (range: 27.5 to 42.0). Disease progression was the primary reason for the end of treatment in 50.0% of subjects. In Cohort 7, 32 subjects were enrolled with 15 subjects (46.9%) ongoing in the treatment phase, with a median follow-up of 10.0 months (range: 6.3 to 15.2). Disease progression was the primary reason for the end of treatment in 25.0% of subjects.

So, at the time of this DCO (Sep. 2020) 33 out of 160 subjects (20.6%) included in any of the four key cohorts (C4, C5b, C6, C7) for this application are still on treatment. The main reasons for treatment discontinuation, consistent in each cohort, were disease progression (80/160, 50%) and adverse events (28/160, 17.5%). Given the high proportion of patients with treatment ongoing (mainly in the expansion Cohorts 6 and 7) at the time of this data cut-off, which was conducted barely a year ago, an update of the main efficacy results was requested during the procedure (this update is presented at the end of the efficacy results).

- **Recruitment**

For Cohort 4, the enrolment period was from April 11st 2016 to April 5th 2018. For Cohort 5b, the enrolment period was from March 20th 2017 to June 6th 2018. The two expansion cohorts (Cohort 6 and Cohort 7) were initiated upon enrolment completion of Cohort 4 and Cohort 5b, respectively. Enrolment periods were from 29-Jun-18 to 31-May-19 for Cohort 6 and from 13-Jun-19 to 12-Mar-20 for Cohort 7.

- **Conduct of the study**

The study protocol was amended 6 times. Since the primary efficacy analysis of MET mutated NSCLC cohorts, the protocol was not amended.

Table 30. List of protocols, protocol amendments and post text supplements

Document	Effective Date
Original Protocol	21-Jan-2015
Amended Protocol Version 01 (track change version)	27-Feb-2015
Amended Protocol Version 02 (track change version)	11-Sep-2015
Amended Protocol Version 03 (track change version)	28-July-2016
Amended Protocol Version 04 (track change version)	17-Nov-2016
Amended Protocol Version 05 (track change version)	13-Feb-2018
Amended Protocol Version 06 (track change version)	28-Feb-2019
Final Protocol Version 06 (clean version)	28-Feb-2019

Amendment 1 was released at a time when no patients have been screened or treated in the study and consisted of indicating that assessment of ALK rearrangement determined with a validated test should be part of the non-squamous NSCLC patient's standard of care, such as the EGFR mutation testing. The inclusion criterion 3 was amended to include ALK-negative rearrangement status.

Amendment 2 was implemented when a total of 5 patients had been enrolled in the study. The main purpose of this amendment was to implement a fourth cohort (Cohort 4) to the study design in light of the emerging data showing that NSCLC patients harbouring MET mutations can benefit from the treatment with MET inhibitors.

Amendment 3 was implemented when a total of 148 patients had been enrolled in the study. The main purpose of this amendment was to: a) Further investigate and better characterize the optimal GCN as predictor of response to INC280 by implementing two sub-cohorts within the high MET amplified Cohort 1 [gene copy number (GCN) ≥ 6] and, b) remove the restrictions on the use of proton pump inhibitors (PPIs) as concomitant medications

Amendment 4 was implemented as of 15-Nov-2016, a total of 157 patients have been enrolled in the study (Cohorts 1a, 1b, e, 3 and 4), and cohort 3 has been suspended due to futility based on the planned interim analyses as outlined in the protocol. The main purpose of this amendment was to implement a new Cohort 5 to investigate the safety and antitumor activity of INC280 in treatment-naïve patients for advanced/metastatic disease (stage IIIB or IV) NSCLC harbouring MET exon 14 skipping mutations (regardless of MET amplification) or very high MET gene amplification (GCN ≥ 10 without MET mutations). Cohort 5: Treatment-naïve patients with MET dysregulation: a) Sub-cohort 5a: Patients with

a MET GCN ≥10 (without MET mutations), b) Sub-cohort 5b: Patients with MET mutations regardless of MET GCN

Amendment 5 was implemented when a total of 269 patients have been enrolled in the study. The main purpose of this amendment was: a) To update the exclusion criteria, the list of prohibited medications, the list of medications to be used with caution and the criteria for dose modifications based on the latest INC280 clinical data as per [Investigator's Brochure edition 9] with primary focus on Pneumonitis/ILD events that have been reported with INC280 monotherapy, and results from the Clinical Pharmacology DDI studies, and b) To introduce a new expansion Cohort 6 for enrolment of approximately additional 30 patients with advanced NSCLC pre-treated with one prior line of systemic therapy harbouring either MET amplification (GCN≥10) or MET mutations (irrespective of MET GCN).

Amendment 6 was implemented when a total of 327 patients have been enrolled in the study. Cohort/ Sub-cohort 1b, 2 and 3 were closed for futility. Cohort/Sub-cohort 1a, 4 and 5b are fully enrolled and closed for recruitment. Enrolment in Sub-cohort 5a has been discontinued and in scope of this protocol amendment. Cohort 6 is open for enrolment of patients with MET mutations regardless of MET GCN.

The purpose of this amendment is to: a) Implement a new expansion Cohort 7 for the enrolment of approximately additional 27 treatment-naïve patients with advanced NSCLC harbouring MET exon 14 skipping mutations (regardless of MET GCN, b) Close the recruitment of GCN ≥ 10 NSCLC patients in Sub-cohort 5a and Cohort 6 due to enrolment hurdles and to very low prevalence of patients with GCN≥ 10, c) Increase Cycle 1 Day 1 (C1D1) blood collection to 3 x 10 mL from 2 x 10 mL. Collection of additional 10 mL blood will provide adequate plasma volume for both circulating tumour DNA (ctDNA) Companion Diagnostic (CDx) development and exploratory baseline testing (i.e. characterization of baseline mutations prior to treatment) and, d) Implement an additional on-treatment blood sample collection (2 x 10 mL) at C3D1 to allow insight into the mechanism of resistance to INC280 therapy.

- **Protocol deviations**

Protocol deviations were commonly observed across all cohorts, with 253 subjects (67.8%) having at least one protocol deviation. Protocol deviations leading to exclusion from per protocol set were observed in 13 subjects (3.5%).

Overall protocol deviations related to COVID-19 pandemic were observed in 28 of 373 subjects (7.5%):

-For 17 subjects (4.6%) visit was performed, however not performed at study site (i.e. at an outside facility) or was performed remotely.

-For 13 subjects (3.5%) assessment or procedure were performed, however not performed as per protocol (i.e. at outside facility, local lab, remote collection of PRO, etc..

-For 12 subjects (3.2%) assessment or procedure were missed due to COVID-19 pandemic

-For 8 subjects (2.1%), there was a change of drug supply method (drug dispensed for more than one visit or drug was delivered directly to subjects' home).

-For 7 subjects (1.9%) the entire schedule visit was missed and no visit activities took place

-For 1 subjects (0.3%) there was a GCP compliance issue related to COVID-19 (tumor assessments were performed less frequent as subject was commuting long distance and was reducing travel due to COVID-19 pandemic).

Protocol deviations were commonly observed across all cohorts, with 253 subjects (67.8%) having at least one protocol deviation. Protocol deviations leading to exclusion from per protocol set were observed in 13 subjects (3.5%). Protocol deviations due to COVID19 pandemic were reported for 28 out of 373 patients (7.5%), in 8 subjects meaning the missing of a complete visit activities or less frequent visits

during the trial. Even if the reasoning behind these deviations is well understood and justified, the applicant was invited to discuss on the extent to what the postponement or missing of evaluation visits might have impacted on the estimation of the antitumoral efficacy of capmatinib. The applicant clarified that of a total of 8 subjects that missed complete visit activities (7 subjects with a reported PD "Assessment/ procedure missed due to COVID-19, PD ID: OTH28" and 1 subject with a reported PD "GPC compliance, PD ID OTH01"), there is potential impact on DOR/PFS analysis due to missed tumour evaluation only for one subject (Subject A2201-1400-015), where a longer DOR/PFS time may have been reported (~6 weeks longer if PD had been reported at the time of missed tumour assessment). A sensitivity analysis showed that the potential impact on efficacy estimation based on PDs related to COVID-19 is negligible**.**

There were no changes in the planned analyses.

- **Baseline data**

Demographic and Disease Characteristics

Table 31. Demographic and baseline characteristics (FAS)

	MET-mutated, pretreated			MET-mutated, treatment-naïve			All Mutant subjects	
Demographic variable	**Cohort 4 (2/3L) N=69**	**Cohort 6 (2L) N=31**	**All subjects (2/3L) N=100**	**Cohort 5b (1L) N=28**	**Cohort 7 (1L) N=32**	**All subjects (1L) N=60**	**(Cohorts 4+6+5b+7) N=160**	**All subjects N=373**
Age (years)								
n	69	31	100	28	32	60	160	373
Mean	71.0	69.0	70.4	72.4	73.3	72.9	71.3	65.7
SD	8.32	6.29	7.78	7.02	8.35	7.70	7.82	10.19
Median	71.0	69.0	70.0	71.0	73.0	72.5	71.0	67.0
Minimum	49.0	49.0	49.0	57.0	48.0	48.0	48.0	33.0
Maximum	90.0	81.0	90.0	86.0	86.0	86.0	90.0	90.0
Age category (years) -n (%)								
<65	14 (20.3)	4 (12.9)	18 (18.0)	3 (10.7)	3 (9.4)	6 (10.0)	24 (15.0)	147 (39.4)
≥65-<75	31 (44.9)	22 (71.0)	53 (53.0)	14 (50.0)	15 (46.9)	29 (48.3)	82 (51.3)	157 (42.1)
≥75-<85	20 (29.0)	5 (16.1)	25 (25.0)	10 (35.7)	12 (37.5)	22 (36.7)	47 (29.4)	60 (16.1)
≥85	4 (5.8)	0	4 (4.0)	1 (3.6)	2 (6.3)	3 (5.0)	7 (4.4)	9 (2.4)
Sex -n (%)								
Female	40 (58.0)	16 (51.6)	56 (56.0)	18 (64.3)	23 (71.9)	41 (68.3)	97 (60.6)	164 (44.0)
Male	29 (42.0)	15 (48.4)	44 (44.0)	10 (35.7)	9 (28.1)	19 (31.7)	63 (39.4)	209 (56.0)
Race -n (%)								
Caucasian	49 (71.0)	24 (77.4)	73 (73.0)	24 (85.7)	26 (81.3)	50 (83.3)	123 (76.9)	281 (75.3)
Asian	19 (27.5)	5 (16.1)	24 (24.0)	4 (14.3)	3 (9.4)	7 (11.7)	31 (19.4)	84 (22.5)
Black	0	1 (3.2)	1 (1.0)	0	1 (3.1)	1 (1.7)	2 (1.3)	3 (0.8)
Native American	1 (1.4)	1 (3.2)	2 (2.0)	0	0	0	2 (1.3)	2 (0.5)
Other	0	0	0	0	2 (6.3)	2 (3.3)	2 (1.3)	2 (0.5)
Unknown	0	0	0	0	0	0	0	1 (0.3)
Ethnicity -n (%)								
Chinese	2 (2.9)	1 (3.2)	3 (3.0)	0	1 (3.1)	1 (1.7)	4 (2.5)	10 (2.7)
East Asian	4 (5.8)	2 (6.5)	6 (6.0)	1 (3.6)	0	1 (1.7)	7 (4.4)	20 (5.4)
Hispanic Or Latino	2 (2.9)	2 (6.5)	4 (4.0)	1 (3.6)	0	1 (1.7)	5 (3.1)	23 (6.2)
Japanese	11 (15.9)	2 (6.5)	13 (13.0)	2 (7.1)	1 (3.1)	3 (5.0)	16 (10.0)	46 (12.3)
Mixed Ethnicity	2 (2.9)	1 (3.2)	3 (3.0)	0	0	0	3 (1.9)	4 (1.1)
Russian	1 (1.4)	4 (12.9)	5 (5.0)	4 (14.3)	3 (9.4)	7 (11.7)	12 (7.5)	15 (4.0)
South Asian	1 (1.4)	0	1 (1.0)	0	1 (3.1)	1 (1.7)	2 (1.3)	3 (0.8)
Southeast Asian	0	0	0	0	0	0	0	1 (0.3)
West Asian	0	0	0	0	0	0	0	5 (1.3)
Other	35 (50.7)	16 (51.6)	51 (51.0)	18 (64.3)	18 (56.3)	36 (60.0)	87 (54.4)	200 (53.6)
Unknown	11 (15.9)	3 (9.7)	14 (14.0)	2 (7.1)	8 (25.0)	10 (16.7)	24 (15.0)	46 (12.3)
ECOG performance status -n (%)								
0	16 (23.2)	10 (32.3)	26 (26.0)	7 (25.0)	7 (21.9)	14 (23.3)	40 (25.0)	107 (28.7)
1	52 (75.4)	21 (67.7)	73 (73.0)	21 (75.0)	25 (78.1)	46 (76.7)	119 (74.4)	265 (71.0)
≥2	1 (1.4)	0	1 (1.0)	0	0	0	1 (0.6)	1 (0.3)
Smoking history -n (%)								
Never smoked	40 (58.0)	19 (61.3)	59 (59.0)	18 (64.3)	20 (62.5)	38 (63.3)	97 (60.6)	129 (34.6)
Ex-smoker	27 (39.1)	10 (32.3)	37 (37.0)	9 (32.1)	11 (34.4)	20 (33.3)	57 (35.6)	205 (55.0)
Current smoker	2 (2.9)	2 (6.5)	4 (4.0)	1 (3.6)	1 (3.1)	2 (3.3)	6 (3.8)	39 (10.5)

2/3L = subjects with one or two prior systemic therapies (pretreated subjects), 1L = subjects with no prior systemic therapy (treatment-naïve).

Table 32. Disease history by cohort (Full analysis set)

	MET-mutated, pretreated			MET-mutated, treatment-naïve			All Mutant subjects (Cohorts 4+6+5b+7)	All subjects
Disease history	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All subjects (2/3L) N=100	Cohort 5b (1L) N=28	Cohort 7 (1L) N=32	All subjects (1L) N=60	N=160	N=373
Histology/Cytology -n (%)								
Adenocarcinoma	53 (76.8)	25 (80.6)	78 (78.0)	25 (89.3)	29 (90.6)	54 (90.0)	132 (82.5)	308 (82.6)
Undifferentiated carcinoma	1 (1.4)	0	1 (1.0)	0	0	0	1 (0.6)	7 (1.9)
Squamous cell carcinoma	6 (8.7)	4 (12.9)	10 (10.0)	2 (7.1)	1 (3.1)	3 (5.0)	13 (8.1)	33 (8.8)
Adenosquamous cell carcinoma	2 (2.9)	0	2 (2.0)	0	0	0	2 (1.3)	5 (1.3)
Large cell carcinoma	1 (1.4)	1 (3.2)	2 (2.0)	0	1 (3.1)	1 (1.7)	3 (1.9)	8 (2.1)
Carcinosarcoma	1 (1.4)	0	1 (1.0)	0	0	0	1 (0.6)	3 (0.8)
Other	5 (7.2)	1 (3.2)	6 (6.0)	1 (3.6)	1 (3.1)	2 (3.3)	8 (5.0)	9 (2.4)
Metastatic site of cancer -n (%)								
Adrenal	11 (15.9)	6 (19.4)	17 (17.0)	6 (21.4)	6 (18.8)	12 (20.0)	29 (18.1)	77 (20.6)
Bone	41 (59.4)	21 (67.7)	62 (62.0)	16 (57.1)	17 (53.1)	33 (55.0)	95 (59.4)	172 (46.1)
Brain	10 (14.5)	7 (22.6)	17 (17.0)	3 (10.7)	6 (18.8)	9 (15.0)	26 (16.3)	97 (26.0)
Liver	16 (23.2)	7 (22.6)	23 (23.0)	4 (14.3)	3 (9.4)	7 (11.7)	30 (18.8)	70 (18.8)
Lung	0	0	0	1 (3.6)	0	1 (1.7)	1 (0.6)	1 (0.3)
Lymph node	46 (66.7)	21 (67.7)	67 (67.0)	16 (57.1)	17 (53.1)	33 (55.0)	100 (62.5)	260 (69.7)
None	1 (1.4)	0	1 (1.0)	0	0	0	1 (0.6)	1 (0.3)
Other	54 (78.3)	23 (74.2)	77 (77.0)	20 (71.4)	21 (65.6)	41 (68.3)	118 (73.8)	273 (73.2)
Number of metastatic sites* -n (%)								
0	1 (1.4)	0	1 (1.0)	0	0	0	1 (0.6)	1 (0.3)
1	5 (7.2)	1 (3.2)	6 (6.0)	3 (10.7)	7 (21.9)	10 (16.7)	16 (10.0)	38 (10.2)
2	10 (14.5)	9 (29.0)	19 (19.0)	11 (39.3)	6 (18.8)	17 (28.3)	36 (22.5)	77 (20.6)
3	14 (20.3)	8 (25.8)	22 (22.0)	3 (10.7)	7 (21.9)	10 (16.7)	32 (20.0)	78 (20.9)
>3	39 (56.5)	13 (41.9)	52 (52.0)	11 (39.3)	12 (37.5)	23 (38.3)	75 (46.9)	179 (48.0)
Stage at initial diagnosis -n (%)								
IA	2 (2.9)	1 (3.2)	3 (3.0)	0	2 (6.3)	2 (3.3)	5 (3.1)	14 (3.8)
IB	5 (7.2)	1 (3.2)	6 (6.0)	2 (7.1)	1 (3.1)	3 (5.0)	9 (5.6)	17 (4.6)
IIA	3 (4.3)	1 (3.2)	4 (4.0)	0	1 (3.1)	1 (1.7)	5 (3.1)	12 (3.2)
IIB	7 (10.1)	1 (3.2)	8 (8.0)	2 (7.1)	0	2 (3.3)	10 (6.3)	16 (4.3)
IIIA	2 (2.9)	2 (6.5)	4 (4.0)	2 (7.1)	1 (3.1)	3 (5.0)	7 (4.4)	38 (10.2)
IIIB	9 (13.0)	4 (12.9)	13 (13.0)	5 (17.9)	1 (3.1)	6 (10.0)	19 (11.9)	36 (9.7)
IV	41 (59.4)	21 (67.7)	62 (62.0)	17 (60.7)	26 (81.3)	43 (71.7)	105 (65.6)	239 (64.1)
Missing	0	0	0	0	0	0	0	1 (0.3)
Time since initial diagnosis of primary site to the first study treatment (months)								
n	69	31	100	28	32	60	160	373
Mean	17.4	10.8	15.4	9.4	7.2	8.2	12.7	15.8
SD	24.65	8.79	21.22	16.56	13.63	14.98	19.38	18.87
Median	11.1	7.6	10.4	2.2	2.2	2.2	7.0	10.6
Minimum	1.6	2.3	1.6	0.6	0.9	0.6	0.6	0.6
Maximum	176.4	45.8	176.4	80.8	71.5	80.8	176.4	176.4
Stage at study entry -n (%)								
IIIB	2 (2.9)	0	2 (2.0)	0	0	0	2 (1.3)	6 (1.6)
IV	67 (97.1)	31 (100)	98 (98.0)	28 (100)	32 (100)	60 (100)	158 (98.8)	367 (98.4)
Number of target lesions at baseline based on BIRC assessment -n (%)								
0	1 (1.4)	2 (6.5)	3 (3.0)	1 (3.6)	0	1 (1.7)	4 (2.5)	12 (3.2)
1	25 (36.2)	10 (32.3)	35 (35.0)	8 (28.6)	4 (12.5)	12 (20.0)	47 (29.4)	96 (25.7)
2	23 (33.3)	10 (32.3)	33 (33.0)	7 (25.0)	12 (37.5)	19 (31.7)	52 (32.5)	119 (31.9)
3	13 (18.8)	6 (19.4)	19 (19.0)	5 (17.9)	12 (37.5)	17 (28.3)	36 (22.5)	88 (23.6)
4	5 (7.2)	1 (3.2)	6 (6.0)	6 (21.4)	4 (12.5)	10 (16.7)	16 (10.0)	40 (10.7)
5	2 (2.9)	2 (6.5)	4 (4.0)	1 (3.6)	0	1 (1.7)	5 (3.1)	18 (4.8)

* Using metastatic sites as collected in CRF page of diagnosis and extent of cancer.
Some metastatic sites are grouped together (Adrenal, Lymph nodes, Bone, Brain sites).
2/3L = subjects with one or two prior systemic therapies (pretreated subjects), 1L = subjects with no prior systemic therapy (treatment-naïve)

Subjects with MET-mutated NSCLC (Cohorts 4, 5b, 6 and 7) were older (median age: 71 years, 33.7% patients older than 75 years, 85% older than 65 years) than non-MET mutated subjects (Cohorts 1a, 1b, 2, 3, and 5a), with a predominance of females (60.6%) and never-smokers (60.6%). The study

included patients with an ECOG PS of 0 (25.0%) and 1 (74.4%), and 1 patient with an ECOG PS of 2. Adenocarcinoma was reported as the primary histology (82.5%). The pre-treated subjects showed greater disease extent than the treatment-naïve subjects; for Cohorts 5b and 7 38.3% had > 3 metastatic sites (brain lesions in 15.0%). For the pre-treated setting (Cohorts 4 and 6), 52.0% had > 3 metastatic sites (brain lesions 17.0%).

When analysing each cohort individually, it is noted that cohort expansion 6 included a slightly less severe/advanced study population than Cohort 4, based on the number of prior treatments (1 or 2 for cohort 4 vs. only 1 prior line for Cohort 6), median age, proportion of patients >75 years, the ECOG PS score, and number of prior metastatic sites. When interpreting the study results, these differences should be carefully considered.

Demographic characteristics were rather similar between Cohort 5b and 7 (treatment naïve), and the same could be said for baseline disease characteristics. Therefore, pooling these two cohorts appears well justified.

Demographics and disease characteristics were representative of the population of adult subjects with EGFR wt advanced NSCLC, and overall consistent with those reported in published case series of patients with METmut NSCLC. The only exception is the proportion of patients with brain metastasis, lower than those described in published reports (15-17% vs. 20-40%, respectively).

Prior therapies

Table 33. Prior antineoplastic therapy – Medication, by cohort (Full analysis set)

	MET-mutated, pretreated			
Characteristic – n (%)	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All subjects (2/3L) N=100	All subjects N=373
Prior antineoplastic regimens				
No	0	0	0	70 (18.8)
Yes	69 (100)	31 (100)	100 (100)	303 (81.2)
Number of prior antineoplastic lines*				
0	0	0	0	75 (20.1)
1	51 (73.9)	30 (96.8)	81 (81.0)	189 (50.7)
2	16 (23.2)	0	16 (16.0)	105 (28.2)
3	2 (2.9)	1 (3.2)	3 (3.0)	4 (1.1)
Therapy type as first line				
Chemotherapy (CT)	61 (88.4)	26 (83.9)	87 (87.0)	282 (75.6)
Platinum based CT	57 (82.6)	25 (80.6)	82 (82.0)	269 (72.1)
Platinum-doublet based CT	56 (81.2)	25 (80.6)	81 (81.0)	268 (71.8)
Single agent CT (non-platinum based)	4 (5.8)	0	4 (4.0)	12 (3.2)
Combination CT (non-platinum based)	0	1 (3.2)	1 (1.0)	1 (0.3)
Immunotherapy (IO)	9 (13.0)	12 (38.7)	21 (21.0)	26 (7.0)
Targeted therapy	3 (4.3)	2 (6.5)	5 (5.0)	35 (9.4)
Therapy type as second line				
Chemotherapy (CT)	8 (11.6)	0	8 (8.0)	68 (18.2)
Platinum based CT	5 (7.2)	0	5 (5.0)	34 (9.1)
Platinum-doublet based CT	5 (7.2)	0	5 (5.0)	33 (8.8)
Single agent CT (non-platinum based)	3 (4.3)	0	3 (3.0)	27 (7.2)
Combination CT (non-platinum based)	0	0	0	7 (1.9)
Immunotherapy (IO)	10 (14.5)	1 (3.2)	11 (11.0)	33 (8.8)

Targeted therapy	0	0	0	15 (4.0)
Therapy type as 3rd line				
Chemotherapy (CT)	2 (2.9)	1 (3.2)	3 (3.0)	3 (0.8)
Platinum based CT	0	1 (3.2)	1 (1.0)	1 (0.3)
Platinum-doublet based CT	0	1 (3.2)	1 (1.0)	1 (0.3)
Single agent CT (non-platinum based)	2 (2.9)	0	2 (2.0)	2 (0.5)
Immunotherapy (IO)	0	0	0	1 (0.3)
Therapy type regardless the line				
Chemotherapy (CT)	65 (94.2)	26 (83.9)	91 (91.0)	289 (77.5)
Platinum based CT	61 (88.4)	25 (80.6)	86 (86.0)	279 (74.8)
Platinum-doublet based CT	60 (87.0)	25 (80.6)	85 (85.0)	278 (74.5)
Single agent CT (non-platinum based)	9 (13.0)	0	9 (9.0)	40 (10.7)
Combination CT (non-platinum based)	0	1 (3.2)	1 (1.0)	8 (2.1)
Immunotherapy (IO)	19 (27.5)	13 (41.9)	32 (32.0)	60 (16.1)
Targeted therapy	3 (4.3)	2 (6.5)	5 (5.0)	45 (12.1)
Therapy type at last treatment**				
Chemotherapy	55 (79.7)	19 (61.3)	74 (74.0)	239 (64.1)
Immunotherapy	13 (18.8)	12 (38.7)	25 (25.0)	50 (13.4)
Targeted therapy	1 (1.4)	0	1 (1.0)	12 (3.2)
Other	0	0	0	2 (0.5)
Setting at last treatment				
Adjuvant	4 (5.8)	1 (3.2)	5 (5.0)	18 (4.8)
Neoadjuvant	0	0	0	3 (0.8)
Therapeutic	64 (92.8)	30 (96.8)	94 (94.0)	281 (75.3)
Palliative	1 (1.4)	0	1 (1.0)	1 (0.3)

*Neo-adjuvant and adjuvant systematic therapies were counted as one prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.
**The medication therapy type of any combination therapy will be classified in the following order: Immunotherapy> Chemotherapy > Biologic therapy > Targeted therapy > Hormonal therapy.
Last treatment was defined as the Last treatment prior to the first dose.
2/3L = subjects with one or two prior systemic therapies (pretreated subjects), 1L = subjects with no prior systemic therapy (treatment-naïve).

Table 34. Prior antineoplastic therapy – Overall, by cohort (Full analysis set)

Characteristic	Cohort 4 (2/3L, Mutant) N=69 n (%)	Cohort 6 (2L, Mutant) N=31 n (%)	All subjects (2/3L, Mutant) N=100 n (%)	All subjects N=373 n (%)
Best response to last therapy				
Complete response (CR)	0	0	0	2 (0.5)
Partial response (PR)	7 (10.1)	5 (16.1)	12 (12.0)	41 (11.0)
Stable disease (SD)	14 (20.3)	4 (12.9)	18 (18.0)	66 (17.7)
Progressive disease (PD)	12 (17.4)	13 (41.9)	25 (25.0)	75 (20.1)
Unknown	5 (7.2)	1 (3.2)	6 (6.0)	11 (2.9)
Not applicable	29 (42.0)	7 (22.6)	36 (36.0)	129 (34.6)
Partial response (PR)/Not applicable (Radiotherapy)	0	0	0	2 (0.5)
Progressive disease (PD)/Not applicable (Radiotherapy)	1 (1.4)	1 (3.2)	2 (2.0)	3 (0.8)
Stable disease (SD)/Not applicable (Radiotherapy)	1 (1.4)	0	1 (1.0)	3 (0.8)

* A subject may have multiple settings. Any prior antineoplastic therapy includes subjects who have had medication, radiotherapy or surgery (non-biopsy).
- Medication: other therapy setting corresponds to Medication in setting other than chemotherapy.
- The medication therapy type of any combination therapy was classified in the following order: Immunotherapy> Chemotherapy > Biologic therapy > Targeted therapy > Hormonal therapy.
- Last therapy is based on start date
- Setting at last therapy was set to 'Not applicable' if the type of last therapy is surgery.
- Best response at last therapy was set to 'Not applicable' if the type of last therapy is surgery or radiotherapy.

Of the 100 MET-mutated subjects who had received ≥ 1 line of systematic therapy for advanced disease (Cohorts 4 and 6), 81 subjects (81.0%) received one prior line of systemic therapy-medication for advanced disease, 16 subjects (16.0%) had received two prior lines, and 3 subjects (3.0%) had received 3 prior lines before receiving capmatinib. The majority of subjects (86.0%) received platinum-based chemotherapy prior to entering the study (irrespective of the line). The use of immunotherapy regardless of line of treatment was higher in cohort 6 (41.9% vs 27.5% in Cohort 4, respectively), which might be explained for the increased role of immunotherapy (both in combination with chemotherapy or monotherapy) in first line in the recent years. It is highlighted that the reported best ORR to prior therapy was 10.1% for Cohort 4 and 16.1% for Cohort 6, all being partial responses, which is consistent with available evidence supporting worse responses to SOC in patients with METmut NSCLC.

- **Numbers analysed**

As of the 18-Sep-2020 data cut-off, this study has completed enrolment for all cohorts and enrolled a total of 373 subjects treated with at least one dose of capmatinib 400 mg. The efficacy evaluation for this submission is mainly based on the cohorts of subjects with MET mutations (treatment-naïve Cohorts 5b and 7, pretreated Cohorts 4 and 6), of whom:

-28 and 32 subjects, respectively, were in Cohort 5b and 7 (subjects with MET-mutated NSCLC with no prior systemic therapy for advanced disease), with a total of 60 treatment-naïve subjects;

-69 and 31 subjects, respectively, were in Cohorts 4 and 6 (subjects with MET-mutated NSCLC who were pre-treated with 1 or 2 lines of prior systemic therapy for advanced stage disease), with a total of 100 pre-treated subjects.

The median study follow-up (defined as the time from the start date of study drug to the data cut-off date) was 34.0 months (range: 27.5 to 42.0) and 10.0 months (range: 6.3 to 15.2) for Cohorts 5b and 7, respectively; and 39.7 months (range: 29.5 to 53.3) and 19.5 months (range: 15.7 to 26.7) for Cohorts 4 and 6, respectively.

Table 35. Analysis sets (all treated subjects)

Analysis set	Cohort 4 (2/3L, Mutant) N=69 n (%)	Cohort 6 (2L, Mutant) N=31 n (%)	All subjects (2/3L, Mutant) N=100 n (%)	Cohort 5b (1L, Mutant) N=28 n (%)	Cohort 7 (1L, Mutant) N=32 n (%)	All subjects (1L, Mutant) N=60 n (%)	All Mutant Subjects (Cohorts 4+6+5b+7) N=160 n (%)	All subjects N=373 n (%)
Full Analysis Set	69 (100)	31 (100)	100 (100)	28 (100)	32 (100)	60 (100)	160 (100)	373 (100)
Safety Set	69 (100)	31 (100)	100 (100)	28 (100)	32 (100)	60 (100)	160 (100)	373 (100)

- N is the number of subjects in Full analysis set.
- The Full Analysis Set (FAS) comprises all subjects who received at least one dose of INC280.
- The Safety Set includes all subjects who received at least one dose of INC280.

- **Outcomes and estimation**

Results from Cohorts 4 and 6 (NSCLC pre-treated with MET mutation) and from Cohort 5b and 7 (NSCLC treatment-naïve with MET mutation) as of the **DCO 18-Sep-2020** are described below.

Primary efficacy endpoint: ORR by BIRC assessment

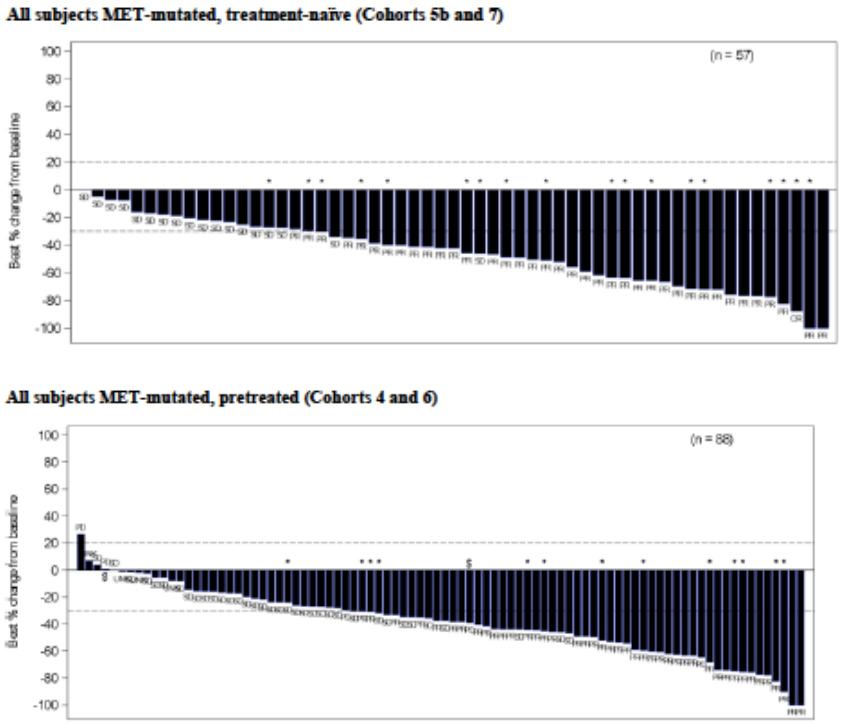
Table 36. Best overall response per BIRC assessment by cohort (Full analysis set) – DCO 18-Sep-2020

	MET-mutated, pretreated			MET-mutated, treatment-naïve		
	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All subjects (2/3L) N=100	Cohort 5b (1L) N=28	Cohort 7 (1L) N=32	All subjects (1L) N=60
Best overall response, n (%)						
Complete response (CR)	0	0	0	1 (3.6)	0	1 (1.7)
Partial response (PR)	28 (40.6)	16 (51.6)	44 (44.0)	18 (64.3)	21 (65.6)	39 (65.0)
Stable disease (SD)	25 (36.2)	11 (35.5)	36 (36.0)	7 (25.0)	11 (34.4)	18 (30.0)
Non-CR/non-PD (NCRNPD)	1 (1.4)	1 (3.2)	2 (2.0)	1 (3.6)	0	1 (1.7)
Progressive disease (PD)	6 (8.7)	0	6 (6.0)	1 (3.6)	0	1 (1.7)
Not evaluable (NE)[b]	9 (13.0)	3 (9.7)	12 (12.0)	0	0	0
Overall response rate (ORR: CR+PR), n (%) (95% CI [a])	**28 (40.6) (28.9, 53.1)**	**16 (51.6) (33.1, 69.8)**	**44 (44.0) (34.1, 54.3)**	**19 (67.9) (47.6,84.1)**	**21 (65.6) (46.8, 81.4)**	**40 (66.7) (53.3, 78.3)**
Disease Control Rate (DCR: CR+PR+SD+NCRNPD), n (%) (95% CI [a])	**54 (78.3) (66.7, 87.3)**	**28 (90.3) (74.2, 98.0)**	**82 (82.0) (73.1, 89.0)**	**27 (96.4) (81.7,99.9)**	**32 (100.0) (89.1, 100.0)**	**59 (98.3) (91.1, 100.0)**

2/3L = subjects with one or two prior systemic therapies (pretreated subjects), 1L = subjects with no prior systemic therapy (treatment-naïve).
[a] Exact binomial 95% Confidence Interval.
[b] Unknown (as per RECIST 1.1) i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks

The majority of the evaluable subjects (with measurable disease at baseline and with at least one valid post-baseline assessment) in Cohorts 5b (96.2%) and 4 (90.0%), and all subjects in Cohorts 6 and 7 showed tumour shrinkage.

Figure 16: **Waterfall plot for best percentage change from baseline in sum of longest diameters per BIRC assessment by cohort (Full analysis set)**



-Supportive analyses for the primary endpoint

ORR per Investigator assessment: The overall concordance rates between BIRC and Investigator assessments of BOR were high (82.1% in Cohort 5b, 75.0% in Cohort 7; 79.7% in Cohort 4, and 80.6% in Cohort 6).

Table 37. Best overall response per Investigator assessment by cohort (Full analysis set) – DCO 18-Sep-2020

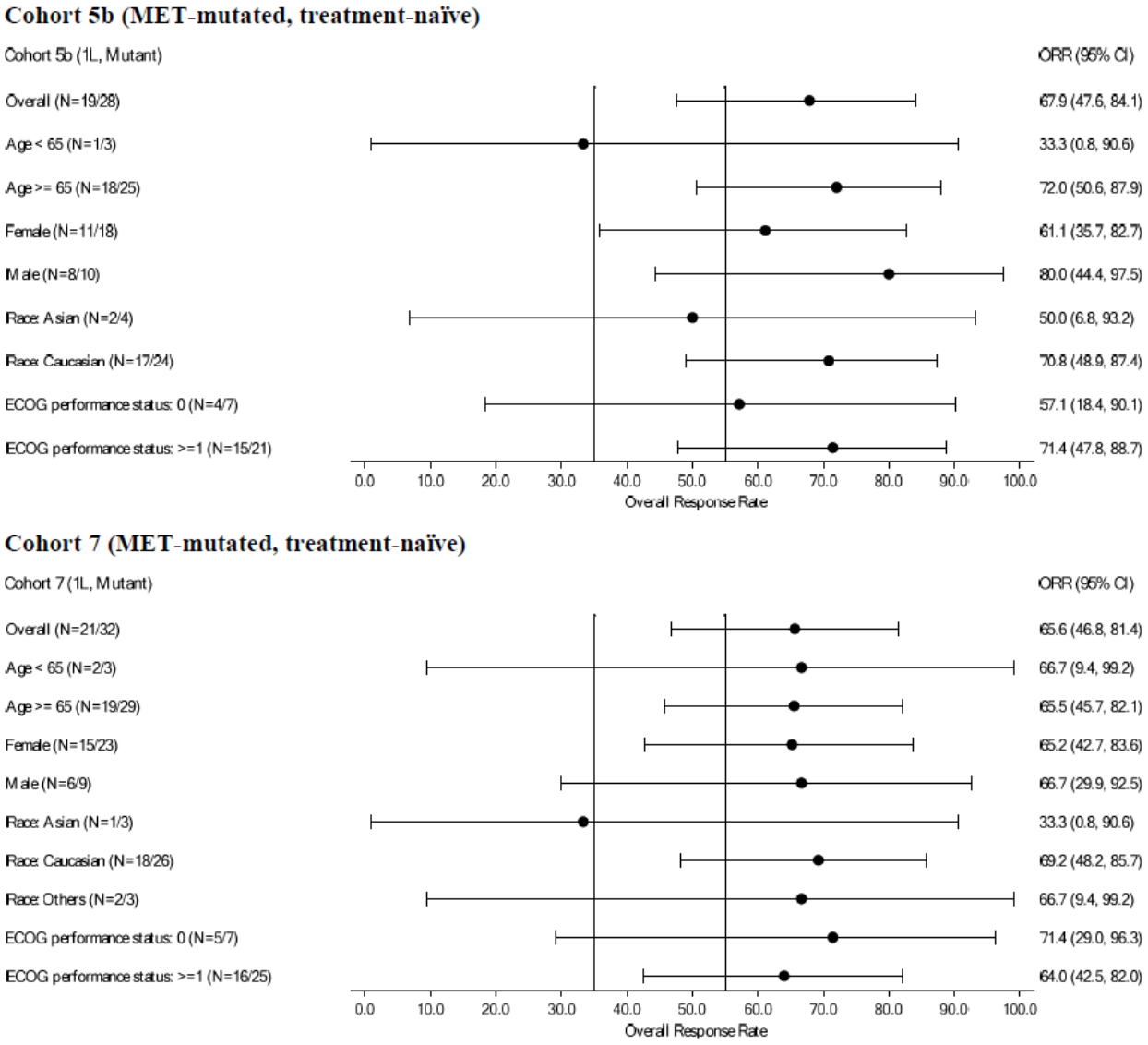
	MET-mutated, pretreated			MET-mutated, treatment-naïve		
	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All subjects (2/3L) N=100	Cohort 5b (1L) N=28	Cohort 7 (1L) N=32	All subjects (1L) N=60
Best overall response, n (%)						
Complete response (CR)	1 (1.4)	0	1 (1.0)	0	1 (3.1)	1 (1.7)
Partial response (PR)	29 (42.0)	14 (45.2)	43 (43.0)	17 (60.7)	17 (53.1)	34 (56.7)
Stable disease (SD)	21 (30.4)	13 (41.9)	34 (34.0)	10 (35.7)	13 (40.6)	23 (38.3)
Non-CR/non-PD (NCRNPD)	2 (2.9)	1 (3.2)	3 (3.0)	0	0	0
Progressive disease (PD)	7 (10.1)	0	7 (7.0)	1 (3.6)	1 (3.1)	2 (3.3)
Not evaluable (NE) [b]	9 (13.0)	3 (9.7)	12 (12.0)	0	0	0
Overall response rate (ORR: CR+PR), n (%) (95% CI [a])	**30 (43.5) (31.6, 56.0)**	**14 (45.2) (27.3, 64.0)**	**44 (44.0) (34.1, 54.3)**	**17 (60.7) (40.6, 78.5)**	**18 (56.3) (37.7, 73.6)**	**35 (58.3) (44.9, 70.9)**
Disease Control Rate (DCR: CR+PR+SD+NCRNPD), n (%) (95% CI [a])	**53 (76.8) (65.1, 86.1)**	**28 (90.3) (74.2, 98.0)**	**81 (81.0) (71.9, 88.2)**	**27 (96.4) (81.7, 99.9)**	**31 (96.9) (83.8, 99.9)**	**58 (96.7) (88.5, 99.6)**

2/3L = subjects with one or two prior systemic therapies (pretreated subjects), 1L = subjects with no prior systemic therapy (treatment-naïve).
[a] Exact binomial 95% confidence interval.
[b] Unknown (as per RECIST 1.1) i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks.

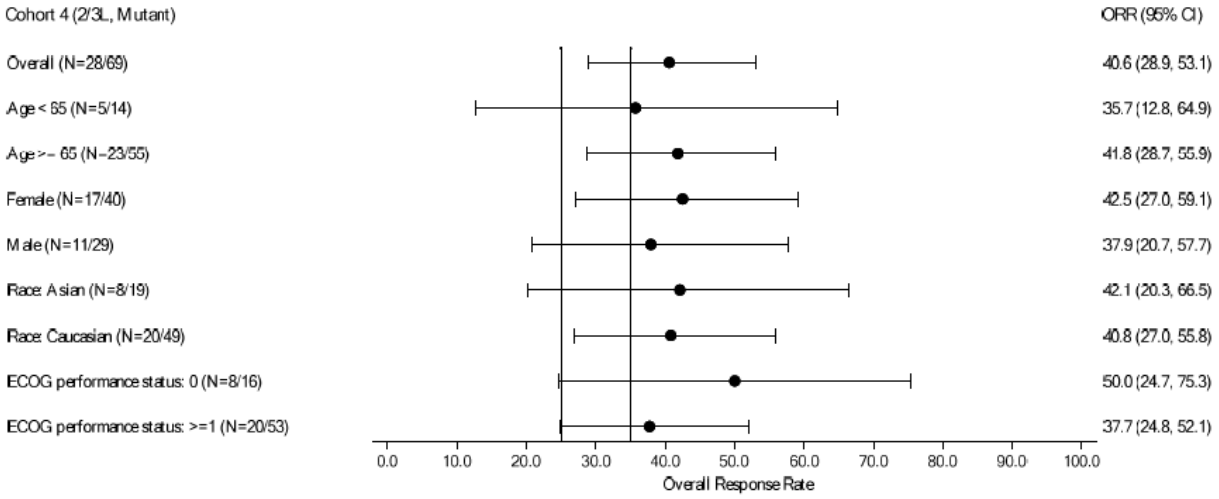
-Subgroup analysis

The consistency in the treatment effect was explored by the subgroup analysis. Within the limitation of the small sample size of each identified subgroup, there was a trend for treatment with capmatinib to be efficacious across all subgroups in treatment-naïve subjects (Cohort 5b and 7) and pre-treated subjects (Cohorts 4 and 6), as assessed by BIRC (Figure 17).

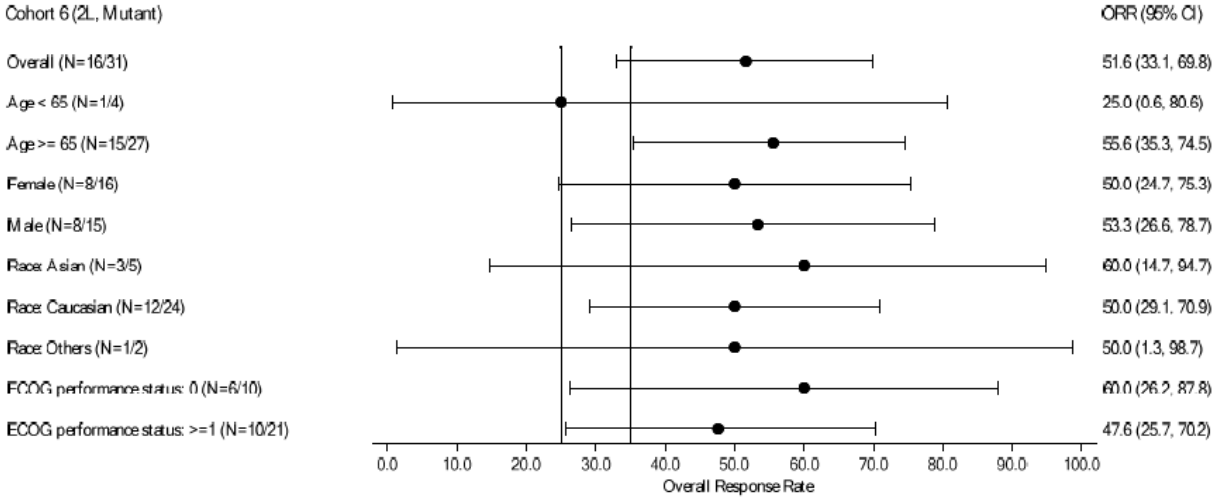
Figure 17. Forest plot of ORR per BIRC assessment by cohort and by subgroup (Full analysis set)



Cohort 4 (MET-mutated, pretreated)



Cohort 6 (MET-mutated, pretreated)



n/N: Number of patients with a confirmed CR or PR/Number of patients who are at the corresponding category.
The vertical lines correspond to the clinically relevant efficacy thresholds (estimate and lower bound of the two sided exact 95% CI).
No statistical assumption for Cohort 6.

Results of secondary efficacy endpoints

-Key secondary endpoint - DOR per BIRC assessment

The median follow-up time for DOR (from the start of response to the date of event/censoring on or prior to the data cut-off) was 11.1 months (range: 2.8 to 31.8) for Cohort 5b, 5.5 months (range: 2.1 to 13.8) for Cohort 7, 9.7 months (range: 2.8 to 30.8) for Cohort 4, and 7.7 months (range: 2.8 to 24.8) for Cohort 6.

Table 38. Summary of duration of response (CR+PR) per BIRC assessment by cohort (Full analysis set)

	MET-mutated, pretreated			MET-mutated, treatment-naïve		
	Cohort 4 (2/3L) N=28	Cohort 6 (2L) N=16	All subjects (2/3L) N=44	Cohort 5b (1L) N=19	Cohort 7 (1L) N=21	All subjects (1L) N=40
No. of events –n (%)	23 (82.1)	11 (68.8)	34 (77.3)	12 (63.2)	5 (23.8)	17 (42.5)
No. of censored –n (%)	5 (17.9)	5 (31.3)	10 (22.7)	7 (36.8)	16 (76.2)	23 (57.5)
Adequate assessment no longer available	0	0	0	1 (5.3)	2 (9.5)	3 (7.5)

Event after ≥ 2 missing assessments	1 (3.6)	0	1 (2.3)	2 (10.5)	0	2 (5.0)
Ongoing without event	4 (14.3)	5 (31.3)	9 (20.5)	3 (15.8)	14 (66.7)	17 (42.5)
Withdrew Consent	0	0	0	1 (5.3)	0	1 (2.5)
Follow-up time for DOR (months)						
Maximum follow-up	30.8	24.8	30.8	31.8	13.8	31.8
Median follow-up	9.7	7.7	9.0	11.1	5.5	7.9
Median time to censoring	27.6	15.3	27.6	24.9	8.0	12.5
Percentiles [95% CI] (month)						
25th	4.22 [2.79, 7.16]	4.86 [2.79, 8.38]	4.22 [2.79, 6.93]	5.55 [2.79, 11.14]	8.41 [2.83, NE]	5.55 [3.55, 9.76]
50th	9.72 [5.55, 12.98]	8.38 [4.17, NE]	9.72 [5.62, 12.98]	12.58 [5.55, NE]	NE [5.52, NE]	12.58 [8.41, NE]
75th	19.52 [10.58, NE]	24.84 [8.38, NE]	19.52 [11.14, NE]	NE [12.58, NE]	NE [8.41, NE]	NE [20.27, NE]
Descriptive summary of DOR (cumulative) -n (%)*						
< 6 months	10 (35.7)	7 (43.8)	17 (38.6)	6 (31.6)	11 (52.4)	17 (42.5)
≥ 6 months	18 (64.3)	9 (56.3)	27 (61.4)	13 (68.4)	10 (47.6)	23 (57.5)
≥ 12 months	9 (32.1)	6 (37.5)	15 (34.1)	9 (47.4)	2 (9.5)	11 (27.5)
≥ 18 months	7 (25.0)	1 (6.3)	8 (18.2)	7 (36.8)	0	7 (17.5)
≥ 24 months	5 (17.9)	1 (6.3)	6 (13.6)	4 (21.1)	0	4 (10.0)

N: The total number of patients with confirmed CR or PR in FAS. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
*The total number of responders is the denominator for percentage (%) calculation.
2/3L = subjects with one or two prior systemic therapies (pretreated subjects), 1L = subjects with no prior systemic therapy (treatment-naïve).

Overall, high tumour responses and durable responses as assessed by BIRC are observed across all four Cohorts.

For pre-treated subjects: in Cohort 4 (2L/3L) median **ORR was 40.6%** (95%CI: 28.9, 53.1), with estimated median DoR 9.7 months (95% CI: 5.55, 12.98); for the expansion Cohort 6 (2L) median **ORR was 51.6%** (95%CI: 33.1, 69.8), and the estimated median DoR was 8.38 months (95% CI: 4.17, NE). Pooled Cohort 4+6 ORR of 44.0% (95%CI: 34.1, 54.3) as assessed by BIRC; the estimated median DOR was **9.72 months** (95% CI: 5.62, 12.98), as assessed by BIRC. All tumour responses were partial responses.

For treatment naïve subjects: in Cohort 5b median **ORR was 67.9%** (95% CI: 47.6, 84.1), and the estimated DoR was 12.58 months (95% CI: 5.55, NE); in the expansion Cohort 7 median **ORR was 65.6%** (95% CI: 46.8, 81.4), and estimated median DoR was not reached. All were partial responses, except 1 CR in Cohort 5b. ORR for pooled Cohort 5b+7 was 66.7% (95% CI: 53.3, 78.3), and the estimated DoR was 12.58 months (95% CI: 8.41, NE).

The majority of the evaluable subjects (with measurable disease at baseline and with at least one valid post-baseline assessment) in Cohorts 5b (96.2%) and 4 (90.0%), and all subjects in Cohorts 6 and 7 showed tumour shrinkage. Consistent results were observed for the subgroups analysed, according to age, gender, ECOG PS 0-1, and by race. Overall, consistent results were observed for the ORR by investigator assessment, with concordance rates ranging from 75% to 82.1%.

Tumour responses were well above the clinically relevant cut-off as defined in the study protocol, with lower ranges of the confidence intervals above 35% for treatment naïve and 25% for pre-treated subjects.

Given the lower antitumoral results observed in NSCLC with MET amplifications and considering that MET amplifications may coexist with MET mutations in the studied population of these 4 METmut cohorts, the applicant is asked to discuss the actual portion of patients with MET amplifications that were included in the studied cohorts and if this might have any impact on the treatment outcomes. The applicant clarified that with protocol amendment 6, recruitment of GCN ≥ 10 (with no METex14 mutation) NSCLC patients into Cohort 5a and Cohort 6 (Group 1) was closed and as of 25-Jan-2019 pre-screening utilizing central

FISH (Fluorescence in Situ Hybridization) testing for MET GCN eligibility was discontinued. Due to that, MET amplification GCN status is not available for patients enrolled in Cohort 7 (n=32, 100%) and for the majority of patients in Cohort 6 (n=16, 52%), for which enrolment was not started or not fully completed, respectively. Because of the limited sample size within each GCN category (GCN <4, ≥4 to <6, ≥6 to 10 and ≥10), especially patients with co-occurrence of METex14 mutation and GCN≥6, it is difficult to draw any robust conclusion on the impact of co-occurrence of MET amplification and MET mutation on antitumoral activity of capmatinib (Table 39). Response to capmatinib was observed in METex14 patients with and without MET amplification.

Table 39. Overall response rate by BIRC by GCN at baseline – MET mutant patients (Full analysis set) DCO 30-Aug-2021

MET amplification status by GCN	Cohort 4 (2/3L, Mutant) N=69		Cohort 6 (2L, Mutant) N=31		Cohort 5b (1L, Mutant) N=28	
	m/n(%)	ORR (%)	m/n(%)	ORR (%)	m/n(%)	ORR (%)
<4	18 (26.1)	3/18 (16.7)	3 (9.7)	1/3 (33.3)	4 (14.3)	1/4 (25.0)
≥4-<6	15 (21.7)	7/15 (46.7)	4 (12.9)	2/4 (50.0)	10 (35.7)	7/10 (70.0)
≥6-<10	17 (24.6)	8/17 (47.1)	7 (22.6)	4/7 (57.1)	3 (10.7)	3/3 (100)
≥10	11 (15.9)	7/11 (63.6)	1 (3.2)	1/1 (100.0)	4 (14.3)	2/4 (50.0)
Missing*	8 (11.6)	3/8 (37.5)	16 (51.6)	8 /16 (50.0)	7 (25.0)	6/7 (85.7)

ORR: overall response rate (subjects with CR or PR as BOR by BIRC).
m/n: number of subjects in the category.
* Results not available or samples not tested due to protocol amendment 6.
Of note, Cohort 7 results are not displayed in this table as MET amplification GCN status is missing for all patients in Cohort 7.

Other Secondary endpoints:

DOR per Investigator assessment

In cohort 5b and 7, the estimated median DOR was 13.83 months (95% CI: 4.27, 25.33) and 9.46 (95% CI: 5.55, NE), respectively. For the 35 responders in the treatment-naïve setting (**Cohorts 5b and 7**), the estimated median DOR per Investigator assessment was 11.93 months (95% CI: 8.41, 24.87).

In cohort 4 and 6, the estimated median DOR was 8.31 months (95% CI: 5.45, 12.06) and 8.38 months (95% CI: 4.17, NE), respectively. For the 44 responders in the 2nd/3rd line pre-treated setting (**Cohorts 4 and 6**), the estimated median DOR per Investigator assessment was 8.38 months (95% CI: 5.55, 13.80).

Disease control rate

In **Cohort 5b**, the DCR was 96.4% (95% CI: 81.7, 99.9) per BIRC and Investigator assessments.
In **Cohort 7**, the DCR was 100% (95% CI: 89.1, 100.0) per BIRC and 96.9% (95% CI: 83.8, 99.9) per Investigator assessment.
In **Cohort 4**, the DCR was 78.3% (95% CI: 66.7, 87.3) per BIRC and 76.8% (95% CI: 65.1, 86.1) per Investigator assessment.
In **Cohort 6**, the DCR was 90.3% (95% CI: 74.2, 98.0) per BIRC and Investigator assessments.

To further increase the precision of the efficacy estimates, efficacy results are **combined** per treatment line:

- Of the 60 MET-mutated subjects in the treatment-naïve setting (**Cohorts 5b and 7**), the DCR was 98.3% (95% CI: 91.1, 100.0) per BIRC and 96.7% (95% CI: 88.5, 99.6) per Investigator assessment.
- Of the 100 MET-mutated subjects in the 2nd/3rd line pre-treated setting (**Cohorts 4 and 6**), the DCR was 82.0% (95% CI: 73.1, 89.0) per BIRC and 81.0% (95% CI: 71.9, 88.2) per Investigator

assessment.

Time to response

Tumour responses to capmatinib were rapid. Across MET-mutated cohorts, time to response per BIRC was ≤ 2 months irrespective of the line of treatment and generally had occurred by the time of first tumour assessment.

In **Cohort 5b**, 68.4% of the responders achieved response within 2 months (by descriptive statistics). The median TTR was 2.69 months (95% CI: 1.38, 6.90) by Kaplan-Meier methodology.
In **Cohort 7**, 66.7% of the responders achieved response within 2 months (by descriptive statistics). The median TTR was 2.79 months (95% CI: 1.45, 7.20) by Kaplan-Meier methodology.
In **Cohort 4**, the majority of the responders (82.1%) achieved response within 2 months (by descriptive statistics). The median TTR was not reached using Kaplan-Meier methodology.
In **Cohort 6**, 62.5% of the responders achieved response within 2 months (by descriptive statistics). The median TTR was 9.66 months (95% CI: 1.51, NE) using Kaplan-Meier methodology.

To further increase the precision of the efficacy estimates, efficacy results are **combined** per treatment line:

- Of the 60 MET-mutated subjects in the treatment-naïve setting (**Cohorts 5b and 7**), 67.5% of the responders achieved response within 2 months (by descriptive statistics). The median TTR was 2.69 months (95% CI: 1.45, 4.24) by Kaplan-Meier methodology.
- Of the 100 MET-mutated subjects in the 2nd/3rd line pre-treated setting (**Cohorts 4 and 6**), 75.0% of the responders achieved response within 2 months (by descriptive statistics). The median TTR was not reached by Kaplan-Meier methodology.

Table 40. Summary of time to response (CR+PR) per BIRC assessment by cohort (Full analysis set) – DCO: 18-Sep-2020

	MET mutated, pretreated			MET mutated, treatment-naïve		
	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All subjects (2/3L) N=100	Cohort 5b (1L) N=28	Cohort 7 (1L) N=32	All subjects (1L) N=60
No. of responders – n (%)	**28 (40.6)**	**16 (51.6)**	**44 (44.0)**	**19 (67.9)**	**21 (65.6)**	**40 (66.7)**
No. of censored – n (%)	**41 (59.4)**	**15 (48.4)**	**56 (56.0)**	**9 (32.1)**	**11 (34.4)**	**20 (33.3)**
Percentiles [95% CI] (months)						
25th	1.41 [1.38, 2.60]	1.41 [1.28, 4.14]	1.41 [1.38, 1.51]	1.36 [1.31, 1.41]	1.41 [1.28, 1.58]	1.38 [1.31, 1.45]
50th	NE [2.76, NE]	9.66 [1.51, NE]	NE [3.84, NE]	2.69 [1.38, 6.90]	2.79 [1.45, 7.20]	2.69 [1.45, 4.24]
75th	NE	NE	NE	NE [2.76, NE]	NE [4.24, NE]	NE [4.24, NE]
% Event probability estimates [95% CI]						
3 months	37.8 [27.4, 50.7]	36.4 [22.0, 56.0]	37.4 [28.6, 47.9]	65.8 [48.3, 82.6]	50.2 [34.5, 68.3]	57.6 [45.4, 70.3]
6 months	42.5 [31.6, 55.3]	43.1 [27.7, 62.4]	42.7 [33.5, 53.2]	65.8 [48.3, 82.6]	64.0 [47.4, 80.3]	65.1 [52.8, 77.1]

2/3L = subjects with one or two prior systemic therapies (pretreated subjects), 1L = subjects with no prior systemic therapy (treatment-naïve).

Time to response per Investigator assessment was consistent with that of the BIRC analysis.

Progression-free survival

The median follow-up time for PFS (from the start of treatment to the date of event/censoring on or prior to the data cut-off) was 11.0 months (range: 1.4 to 33.3) for Cohort 5b, 6.9 months (range: 2.7 to 15.2) for Cohort 7, 4.7 months (range: 0 to 32.0) for Cohort 4, and 6.7 months (range: 0.9 to 26.3) for Cohort 6.

In **Cohort 5b**, the median PFS by BIRC was 12.42 months (95% CI: 8.21, 23.39). Ten subjects (35.7%) were censored including 3 subjects (10.7%) who were ongoing without an event.
In **Cohort 7**, the median PFS by BIRC was 10.84 months (95% CI: 6.87, NE). Eighteen subjects (56.3%) were censored including 14 subjects (43.8%) who were ongoing without an event. PFS data are not yet mature with 14 PFS events (43.8%) reported in 32 subjects.
In **Cohort 4**, the median PFS by BIRC was 5.42 months (95% CI: 4.17, 6.97). Nine subjects (13.0%) were censored including 4 subjects (5.8%) who were ongoing without an event.
In **Cohort 6**, and the median PFS by BIRC was 6.93 months (95% CI: 4.17, 13.34). Nine subjects (29.0%) were censored including 7 subjects (22.6%) who were ongoing without an event.

To further increase the precision of the efficacy estimates, efficacy results are **combined** per treatment line:

- Of the 60 MET-mutated subjects in the treatment-naïve setting (**Cohorts 5b and 7**), the median PFS by BIRC was 12.29 months (95% CI: 8.21, 21.62). Twenty-eight subjects (46.7%) were censored including 17 subjects (28.3%) who were ongoing without an event.
- Of the 100 MET-mutated subjects in the 2nd/3rd line pre-treated setting (**Cohorts 4 and 6**), the median PFS by BIRC was 5.49 months (95% CI: 4.17, 8.11). Eighteen subjects (18.0%) were censored including 11 subjects (11.0%) who were ongoing without an event.

Table 41. Summary of progression-free survival per BIRC assessment by cohort (Full analysis set) – DCO: 18-Sep-2020

	MET-mutated, pretreated			MET-mutated, treatment-naïve		
	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All subjects (2/3L) N=100	Cohort 5b (1L) N=28	Cohort 7 (1L) N=32	All subjects (1L) N=60
No. of events –n (%)	**60 (87.0)**	**22 (71.0)**	**82 (82.0)**	**18 (64.3)**	**14 (43.8)**	**32 (53.3)**
Progression	54 (78.3)	20 (64.5)	74 (74.0)	15 (53.6)	10 (31.3)	25 (41.7)
Death	6 (8.7)	2 (6.5)	8 (8.0)	3 (10.7)	4 (12.5)	7 (11.7)
No. of censored –n (%)	**9 (13.0)**	**9 (29.0)**	**18 (18.0)**	**10 (35.7)**	**18 (56.3)**	**28 (46.7)**
Percentiles [95% CI] (month)						
25th	2.73 [2.30, 4.14]	4.14 [2.76, 5.42]	2.83 [2.66, 4.17]	5.52 [3.19, 9.69]	5.52 [4.01, 7.10]	5.52 [4.30, 8.21]
50th	5.42 [4.17, 6.97]	6.93 [4.17, 13.34]	5.49 [4.17, 8.11]	12.42 [8.21, 23.39]	10.84 [6.87, NE]	12.29 [8.21, 21.62]
75th	12.48 [8.18, 16.79]	20.70 [8.34, NE]	13.34 [10.38, 26.15]	NE [13.86, NE]	NE [10.84, NE]	NE [13.86, NE]
% Event-free probability estimates [95% CI]						
3 months	69.5 [56.8, 79.1]	83.5 [64.8, 92.8]	73.9 [63.9, 81.5]	96.3 [76.5, 99.5]	93.5 [76.6, 98.3]	94.9 [84.9, 98.3]
6 months	41.7 [29.7, 53.3]	56.6 [37.2, 72.1]	46.2 [35.9, 55.9]	73.3 [52.0, 86.3]	70.3 [50.7, 83.3]	71.7 [58.0, 81.6]
9 months	33.9 [22.7, 45.4]	42.5 [24.6, 59.3]	36.5 [26.9, 46.2]	65.2 [43.6, 80.2]	58.4 [38.1, 74.0]	61.3 [46.8, 72.9]
12 months	25.8 [15.9, 36.9]	38.9 [21.6, 55.9]	29.9 [20.9, 39.3]	57.0 [35.8, 73.5]	45.4 [23.9, 64.7]	51.6 [36.9, 64.6]
24 months	12.9 [6.1, 22.4]	23.9 [8.5, 43.5]	16.5 [9.5, 25.2]	26.7 [11.0, 45.5]	NE	25.6 [11.6, 42.2]

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
Event-free probability estimate was the estimated probability that a patient remained event-free up to the specified time point.
Event-free probability estimates were obtained from the Kaplan-Meier survival estimates for all cohorts; Greenwood formula was used for CIs of KM estimates.
2/3L = subjects with one or two prior systemic therapies (pretreated subjects), 1L = subjects with no prior systemic therapy (treatment-naïve).

The PFS results per Investigator assessment were consistent with the results per BIRC assessment. The median PFS per Investigator assessment was 11.99 months (95% CI: 5.52, 16.92) in Cohort 5b, 9.79 months (95% CI: 5.75, 11.89) in Cohort 7, 4.80 months (95% CI: 4.11, 7.75) in Cohort 4 and 6.90 months (95% CI: 5.55, NE) in Cohort 6.

Further, the median PFS per Investigator assessment was 10.84 months (95% CI: 6.74, 14.69) for the 60 MET-mutated subjects in the treatment-naïve setting and 6.60 months (95% CI: 4.70, 8.18) for the 100 MET-mutated subjects in the 2nd/3rd line pre-treated setting.

Overall survival

The median follow-up time for OS (from the start of treatment to the death or last contact date on or prior to the data cut-off date) was 19.9 months (range: 2.3 to 41.8) for Cohort 5b, 9.0 months (range: 2.9 to 15.2) for Cohort 7, 11.5 months (range: 0.5 to 47.7) for Cohort 4, and 14.9 months (range: 0.9 to 26.6) for Cohort 6.

To further increase the precision of the efficacy estimates, efficacy results are **combined** per treatment line:

- Of the 60 MET-mutated subjects in the treatment-naïve setting (**Cohorts 5b and 7**), the median follow-up time for OS was 11.0 months (range: 2.3 to 41.8). The median OS was 20.76 months (95% CI: 12.42, 30.52). Twenty-five deaths (41.7%) were reported and 35 subjects (58.3%) were censored for survival, including 32 alive at the time of the data cut-off and 3 lost to follow-up. The Kaplan-Meier estimated OS rate at 6 months was 91.7% (95% CI: 81.1, 96.4), and at 12 months was 69.4% (95% CI: 53.9, 80.6).
- Of the 100 MET-mutated subjects in the 2nd/3rd line pre-treated setting (**Cohorts 4 and 6**), the median follow-up time for OS was 13.6 months (range: 0.5 to 47.7). The median OS was 14.85 months (95% CI: 11.63, 23.26). Sixty-two deaths (62%) were reported and 38 (38.0%) were censored for survival including 29 alive and 9 lost to follow-up. The Kaplan-Meier estimated OS rate at 6 months was 77.3% (95% CI: 67.6, 84.4), and at 12 months was 58.7% (95% CI: 48.0, 67.9).

Table 42. Summary of overall survival by cohort (Full analysis set) – DCO: 18-Sep-2020

	Cohort 4 (2/3L, Mutant) N=69	Cohort 6 (2L, Mutant) N=31	All subjects (2/3L, Mutant) N=100	Cohort 5b (1L, Mutant) N=28	Cohort 7 (1L, Mutant) N=32	All subjects (1L, Mutant) N=60
No. of events- n(%)	50 (72.5)	12 (38.7)	62 (62.0)	17 (60.7)	8 (25.0)	25 (41.7)
No. of censored - n(%)	19 (27.5)	19 (61.3)	38 (38.0)	11 (39.3)	24 (75.0)	35 (58.3)
Percentiles [95% CI] (months)						
25th	4.80 [3.75, 8.61]	11.63 [4.30, 17.12]	6.64 [4.11, 9.03]	11.91 [3.19, 15.24]	10.55 [6.11, NE]	10.84 [6.60, 12.55]
50th	13.57 [8.61, 22.24]	NE [13.54, NE]	14.85 [11.63, 23.26]	20.76 [12.42, NE]	NE [10.55, NE]	20.76 [12.42, 30.52]
75th	28.78 [23.26, NE]	NE	42.05 [24.97, NE]	NE [29.44, NE]	NE	NE [29.44, NE]
% Event-free probability estimates [95% CI]						
3 months	89.6 [79.4, 94.9]	93.5 [76.6, 98.3]	90.9 [83.2, 95.1]	96.4 [77.2, 99.5]	96.9 [79.8, 99.6]	96.7 [87.3, 99.2]
6 months	71.4 [58.8, 80.7]	90.1 [72.3, 96.7]	77.3 [67.6, 84.4]	89.3 [70.4, 96.4]	93.8 [77.3, 98.4]	91.7 [81.1, 96.4]
9 months	60.5 [47.6, 71.1]	79.7 [60.2, 90.3]	66.5 [56.0, 75.0]	85.7 [66.3, 94.4]	82.6 [62.9, 92.4]	84.4 [72.1, 91.6]
12 months	52.6 [39.9, 63.9]	72.3 [52.0, 85.1]	58.7 [48.0, 67.9]	75.0 [54.6, 87.2]	58.4 [30.2, 78.6]	69.4 [53.9, 80.6]
24 months	33.5 [22.3, 45.1]	54.8 [33.2, 72.0]	37.9 [27.4, 48.3]	49.5 [30.1, 66.3]	NE	47.0 [30.0, 62.3]

- Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
- Event-free probability estimate is the estimated probability that a subject will remain event-free up to the specified time point.
- Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all cohorts; Greenwood formula is used for CIs of KM estimates.

Overall, consistent results were observed for these secondary endpoints as per investigator assessment.

Secondary endpoints results support the primary analysis. It is noted that the onset of response was seen within 2 months for most of the study population. Median PFS and PFS show consistent and promising results, but interpretation should be made with caution given the lack of a control arm.

In response to the D120 LoQ, updated efficacy results were provided with a **cut of date of 30 Aug 2021.**

Table 43. Treatment-naive and previously treated MET-mutated locally advanced or metastatic NSCLC: Efficacy results of the primary analyses by BIRC in patients who received capmatinib in Study A2201 (DCO 30-Aug-2021)

Efficacy parameters	Previously treated patients		Treatment-naive patients	
	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	Cohort 5b (1L) N=28	Cohort 7 (1L) N=32
ORR[a] n(%)	**28 (40.6%)**	**16 (51.6%)**	**19 (67.9%)**	**22 (68.8%)**
(95% CI)[b]	**(28.9, 53.1)**	**(33.1, 69.8)**	**(47.6, 84.1)**	**(50.0, 83.9)**
CR, n (%)	1 (1.4)	0	2 (7.1)	1 (3.1)
PR, n (%)	27 (39.1)	16 (51.6)	17 (60.7)	21 (65.6)
DCR[a] n(%)	54 (78.3)	28 (90.3)	27 (96.4)	32 (100%)
(95% CI)[b]	(66.7, 87.3)	(74.2, 98.0)	(81.7, 99.9)	(89.1, 100.0)
DoR[a]				
N	28	16	19	22
Median, months (95% CI)[c]	9.72 (5.55, 12.98)	9.05 (4.17, NE)	12.58 (5.55, NE)	16.59 # (8.34, NE)
PFS[a]				
Median, months (95% CI)[c]	5.42 (4.17, 6.97)	6.93 (4.17, 13.34)	12.42 (8.21, 23.39)	12.45 (6.87, 20.50)
OS				
Median, months (95% CI)[c]	13.57 (8.61, 22.24)	24.28 (13.54, NE)	20.76 (12.42, NE)	NE # (12.85, NE)

CI: confidence interval; NE: not estimable; CR: complete response; PR: partial response; DoR: duration of response.

ORR (Overall response rate): CR+PR.

DCR (disease control rate) = CR+PR+SD

[a] by BIRC per RECIST v1.1.

[b] Clopper and Pearson exact binomial 95% CI.

[c] Based on Kaplan-Meier estimate.

not mature yet

As requested also an additional sensitivity analyses analysis were provided. For the sensitivity analyses the following rules were taken into account:

- Progression or death after two or more missing assessments" was considered as an event at the date of progression or death.
- An event was considered at the visit date at which clinical progression was determined by the investigator (i.e. event at the "Discontinuation date" at End of Treatment for subjects who discontinued study treatment due to "Progressive disease"), if progression is not confirmed by BIRC.
- An event was considered at the time of the initiation of the new anti-neoplastic therapy.

The results for the pretreated and treatment naive patients are provided below.

Table 44. Summary of duration of response (CR+PR) per BIRC assessment by cohort – Sensitivity analyses - All patients (2/3L, Mutant) (Full analysis set) (DCO 30-Aug-2021)

	Cohort 4 (2/3L, Mutant)		Cohort 6 (2L, Mutant)		All patients (2/3L, Mutant)	
	Primary analysis N=28	Sensitivity analysis N=28	Primary analysis N=16	Sensitivity analysis N=16	Primary analysis N=44	Sensitivity analysis N=44
No. of events n(%)	**23 (82.1)**	**25 (89.3)**	**11 (68.8)**	**12 (75.0)**	**34 (77.3)**	**37 (84.1)**
No. of censored n(%)	**5 (17.9)**	**3 (10.7)**	**5 (31.3)**	**4 (25.0)**	**10 (22.7)**	**7 (15.9)**
Adequate assessment no longer available	1 (3.6)	0	0	0	1 (2.3)	0
Event after ≥ 2 missing assessments	1 (3.6)	0	0	0	1 (2.3)	0
Ongoing without event	3 (10.7)	3 (10.7)	5 (31.3)	4 (25.0)	8 (18.2)	7 (15.9)
Withdrew Consent	0	0	0	0	0	0
Median [95% CI] (month)	9.72 [5.55, 12.98]	9.17 [5.13, 11.20]	9.05 [4.17, NE]	9.05 [4.17, 27.60]	9.72 [5.62, 12.98]	9.17 [5.55, 12.98]
Kaplan-Meier estimates (%) DOR rate [95% CI] at:						
6 months	64.3 [43.8, 78.9]	60.7 [40.4, 76.0]	62.5 [34.9, 81.1]	62.5 [34.9, 81.1]	63.6 [47.7, 75.9]	61.4 [45.4, 73.9]
9 months	56.9 [36.8, 72.8]	50.0 [30.6, 66.6]	50.0 [24.5, 71.0]	50.0 [24.5, 71.0]	54.4 [38.6, 67.7]	50.0 [34.6, 63.6]
12 months	34.2 [17.4, 51.7]	32.1 [16.1, 49.3]	43.8 [19.8, 65.6]	43.8 [19.8, 65.6]	37.8 [23.6, 51.9]	36.4 [22.6, 50.3]
24 months	19.0 [7.0, 35.5]	14.3 [4.5, 29.5]	37.5 [15.4, 59.8]	37.5 [15.4, 59.8]	25.6 [13.7, 39.3]	22.3 [11.4, 35.5]

N: The total number of patients with confirmed CR or PR in FAS. It is the denominator for percentage (%) calculation.

n: Number of patients who are at the corresponding category.

*The total number of responders is the denominator for percentage (%) calculation.

Sensitivity analyses Options per RECIST guidelines V3.1 per protocol:

Option C2(3): Progression or death after two or more missing assessments as an event at the date of progression (or death).

Option E(2): Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim as an event at the date of the discontinuation.

Option F(4): New anticancer therapy given as an event at the date of the initiation of the new anticancer therapy.

Table 45. Summary of duration of response (CR+PR) per BIRC assessment by cohort – Sensitivity analyses - All patients (1L, Mutant) (Full analysis set) (DCO 30-Aug-2021)

	Cohort 5b (1L, Mutant)		Cohort 7 (1L, Mutant)		All patients (1L, Mutant)	
	Primary analysis N=19	Sensitivity analysis N=19	Primary analysis N=22	Sensitivity analysis N=22	Primary analysis N=41	Sensitivity analysis N=41
No. of events n(%)	**12 (63.2)**	**15 (78.9)**	**11 (50.0)**	**15 (68.2)**	**23 (56.1)**	**30 (73.2)**
No. of censored n(%)	**7 (36.8)**	**4 (21.1)**	**11 (50.0)**	**7 (31.8)**	**18 (43.9)**	**11 (26.8)**
Adequate assessment no longer available	1 (5.3)	0	1 (4.5)	0	2 (4.9)	0
Event after ≥ 2 missing assessments	2 (10.5)	0	2 (9.1)	0	4 (9.8)	0
Ongoing without event	3 (15.8)	3 (15.8)	8 (36.4)	7 (31.8)	11 (26.8)	10 (24.4)
Withdrew Consent	1 (5.3)	1 (5.3)	0	0	1 (2.4)	1 (2.4)

	Cohort 5b (1L, Mutant)		Cohort 7 (1L, Mutant)		All patients (1L, Mutant)	
	Primary analysis N=19	**Sensitivity analysis N=19**	**Primary analysis N=22**	**Sensitivity analysis N=22**	**Primary analysis N=41**	**Sensitivity analysis N=41**
Median [95% CI] (month)	12.58 [5.55, NE]	11.14 [5.55, 24.15]	16.59 [8.34, NE]	15.70 [5.75, 19.35]	16.59 [8.41, 22.11]	12.58 [7.75, 19.35]

N: The total number of patients with confirmed CR or PR in FAS. It is the denominator for percentage (%) calculation.

n: Number of patients who are at the corresponding category.

*The total number of responders is the denominator for percentage (%) calculation.

Sensitivity analyses Options per RECIST guidelines V3.1 per protocol:

Option C2(3): Progression or death after two or more missing assessments as an event at the date of progression (or death).

Option E(2): Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim as an event at the date of the discontinuation.

Option F(4): New anticancer therapy given as an event at the date of the initiation of the new anticancer therapy.

As of the DCO (30-Aug-2021), 3 responders (1 in Cohort 4, 1 in Cohort 5b, 1 in Cohort 7) were censored due to "Adequate assessment no longer available" for DOR by BIRC (Table 45). Two responders had a PD documented by the investigator but not confirmed by BIRC.

Intracranial activity in patients with brain metastases – from DCO 18- Sep-2020

In a post hoc analysis for Study A2201 DCO 18-Sep-2020, medical review was performed on BIRC neuroradiologic assessments, evaluating the intracranial shrinkage of target and nontarget brain lesions at each evaluation. Intracranial disease control was defined as subjects with shrinkage or stability in intracranial brain lesions as per medical review. Antineoplastic radiotherapies or surgeries outside of the brain are not considered as antineoplastic therapy for brain assessments. There were 29 subjects with MET exon 14 skipping mutated NSCLC:

-Cohorts 5b and 7 (treatment-naïve, 9 subjects) and Cohorts 4 and 6 (pre-treated, 20 subjects) who had brain lesions by BIRC at baseline. Of those, 28 subjects had data (with baseline tumour assessment and at least one post-baseline tumour assessment) that could be evaluated by the independent neuroradiologic review committee. Demographic characteristic in this subgroup were comparable with the overall population.

-Intracranial activity according to neuroradiologic assessment by BIRC are reported as follows:

- Twenty-five out of 28 evaluable subjects had an intracranial disease control (18/25 subjects had been previously treated and 7/25 subjects were treatment naïve). The other 3 subjects progressed in the brain (2 subjects had been previously treated and 1 subject was treatment naïve).
- Sixteen subjects out of the 28 evaluable subjects showed intracranial lesion shrinkage, of whom 9 had complete disappearance of intracranial lesions (8 subjects had been previously treated and 1 subject was treatment naïve).
- Of the 25 subjects who had intracranial disease control, 11 had received brain radiotherapy before study entry; of the 16 subjects who showed intracranial lesion shrinkage, 6 had received brain radiotherapy before study entry.
- Of the 16 subjects who showed intracranial lesion shrinkage, intracranial lesion shrinkage were observed at the first assessment in 13 subjects, and for the other 3 subjects disease was controlled at the first assessment before the first intracranial lesion shrinkage was shown.

Based on this post hoc analysis, the medical review of neuroradiologic assessments evaluating the intracranial shrinkage of brain lesions at each evaluation, capmatinib shows a promising intracranial activity in patients with brain metastases comparable to the overall population in Study A2201.

This exploratory post hoc analysis shows promising but still limited evidence on the efficacy of capmatinib on brain metastases to make any sound conclusions.

Patient-reported outcomes – from DCO 06-Jan-2020

Measure of health-related quality of life was an exploratory endpoint of Study A2201 and was assessed at baseline and every 6 weeks up until end of treatment using the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires which are reliable and validated measures frequently used in clinical trials of patients with lung cancer.

PRO results are displayed by cohort. Results were scored from 0 to 100 where a change of ≥10 points from baseline is considered to be the minimal clinically important difference. Lower scores indicate reduced symptoms on EORTC QLQ-LC13 and LC13 symptom scales, and higher scores indicate improvement on EORTC QLQ-C30 function scales, and global health status/quality of life and EQ-5D-5L visual analogue scores.

The most recent DCO for PRO results is 06-Jan-2020 as exploratory endpoints were out of scope for the analysis of DCO 18-Sep-2020. Efficacy result for Cohort 7 was out of scope for the analysis of DCO 06-Jan-2020.

Results

Overall, changes from baseline over time, in PRO scores in treatment-naïve subjects (Cohort 5b) and pre-treated subjects (Cohort 4 and Cohort 6) (DCO-06-Jan-2020) were mostly maintained, suggesting no deterioration of symptoms and quality of life of NSCLC subjects with tumours harbouring the MET exon 14 mutation.

--The compliance rate of the eligible subjects completing the EORTC QLQ-C30 with baseline and at least one post-baseline score was 92.2% in Cohort 4, 96.3% in Cohort 5b and 89.7% in Cohort 6.

--The compliance rate of the eligible subjects completing the EORTC QLQ-LC13 and EQ-5D-5L was similar, with baseline and at least one post-baseline score available for 92.1% of subjects in Cohort 4, 96.3% in Cohort 5b and 89.7% in Cohort 6.

EORTC QLQ-C30

Most EORTC QLQ-C30 scales were maintained from baseline in Cohort 4, Cohort 5b and Cohort 6. Subjects in Cohort 4 and Cohort 5b tended to show some improvement over time in emotional functioning and global health status/quality of life (QoL).

The median time to definitive deterioration (TTDD) (by Kaplan-Meier methodology) for the global health status/QoL was 12.39 months (95% CI: 4.21, 19.35) in Cohort 4, 16.62 months (95% CI: 9.66, NE) in Cohort 5b and was not estimable in Cohort 6.

EORTC QLQ-LC13

Overall, the EORTC QLQ-LC13 scales were maintained from baseline for Cohorts 4, 5b, and 6.

Cough improved early, with meaningful improvements observed through cycles (mean change from baseline [SD] at Week 7: Cohort 5b: -13.0 [39.9], Cohort 4: -8.2 [28.4] and Cohort 6: -13.6 [26.6]; Week 25: Cohort 5b: -15.6 [33.0], Cohort 4: -6.0 [31.5] and Cohort 6: -11.1 [30.3]; Week 43: Cohort 5b: -28.2 [26.7], Cohort 4: -10.5 [27.3] and Cohort 6: -38.1 [30.0]).

Time to definitive deterioration (TTDD) in QLQ-LC13 symptoms was the time from treatment initiation to first date of ≥10% symptom change from baseline with no later reduction. The median TTDD (by Kaplan-Meier methodology) for coughing and pain in the chest was not estimable.

EQ-5D-5L

All EQ-5D-5L scales remained unchanged in all Cohort 4, Cohort 5b and Cohort 6, overtime.

Based on these exploratory analyses, capmatinib was associated with improvements in cough, delayed time to lung symptom deterioration, and preserved QoL. Results from this exploratory analysis with data generated in the context of an open label uncontrolled study are not considerable suitable for inclusion in the SmPC. QoL data is difficult to interpret in an open-label single-arm trial given the subjective nature of PROs and the fact that it is not possible to infer how patients would have rated their QoL if they had received alternative treatments or standard of care. Besides, QoL was an exploratory endpoint and there was no detailed description of the analysis plan included in the protocol (e.g., scale of interest, a clear hypothesis, methods for handling missing data). Looking at the number of patients that responded to the QoL questionnaires at each of the follow up timepoints, is appears that the results are based on a small percentage of patients who responded at each timepoint. These patients are likely to be those who responded to treatment and are not representative of the full cohort. It is claimed by the applicant that the baseline level of QoL was maintained over time, and that there were even some improvements observed in some scales (e.g., cough).

- **Ancillary analyses**

NA

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main study 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 46. Summary of Efficacy for trial CINC280A2201– DCO: 18-Sep-2020

Title: A phase II, multicentre, study of oral MET inhibitor INC280 in adult patients with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC).		
Study identifier	CINC280A2201, EudraCT number: 2014-003850-15	
Design	This is a prospectively designed, open-label study to evaluate the efficacy and safety of single-agent INC280 in patients with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-negative rearrangement, advanced (stage III B or IV) NSCLC harbouring MET amplification and/or mutations. 373 subjects were enrolled in the study depending on their MET amplification and/or mutation status and prior treatment status: 69 subjects were enrolled in Cohort 1a, 42 in Cohort 1b, 54 in Cohort 2, 30 in Cohort 3, 69 in Cohort 4, 15 in Cohort 5a, 28 in Cohort 5b, 34 in Cohort 6 (including 31 with MET mutations), and 32 in Cohort 7.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	5 years not applicable not applicable

Hypothesis	• Cohort 4: The null hypothesis will be rejected if ORR ≥ 35% and the lower bound of the two-sided 95% exact confidence interval (95% CI) is >25%. • Cohort 6: No hypothesis testing. • Cohort 5b/7: The null hypothesis will be rejected if ORR ≥ 55% and the lower bound of the two-sided 95% exact CI is >35%.		
Treatments groups	Cohort 4 (2/3L, MET mutant)		Treatment: capmatinib, median duration of treatment: 22.1 weeks, number of treated patients: 69
	Cohort 6 (2L, MET mutant)		Treatment: capmatinib, median duration of treatment: 36.0 weeks, number of treated patients: 31
	Cohort 5b (1L, MET mutant)		Treatment: capmatinib, median duration of treatment: 48.2 weeks, number of treated patients: 28
	Cohort 7 (1L, MET mutant)		Treatment: capmatinib, median duration of treatment: 33.4 weeks, number of treated patients: 32
Endpoints and definitions	Primary endpoint	ORR By BIRC	Overall response rate (ORR) as assessed by BIRC per RECIST 1.1 is defined as the proportion of patients with a best overall response defined as complete response or partial response (CR+PR) by BIRC assessment per RECIST 1.1
	Key Secondary endpoint	DOR by BIRC	DOR as assessed by BIRC per RECIST 1.1 is calculated as the time from the date of the first documented CR or PR by BIRC per RECIST 1.1 to the first documented progression or death due to any cause for patients with PR or CR
	Other secondary endpoint	ORR and DOR by investigator	ORR and DOR per RECIST 1.1 by investigator assessment
	Other secondary endpoint	TTR by BIRC and investigator	Time to response (TTR) is calculated as the time from first dose of INC280 to first documented response (CR+PR) for patients with PR or CR TTR per RECIST 1.1, both by BIRC and investigator
	Other secondary endpoint	DCR by BIRC and investigator	Disease control rate (DCR), calculated as the proportion of patients with best overall response of CR, PR, or SD DCR per RECIST 1.1, both by BIRC and investigator
	Other secondary endpoint	PFS by BIRC and investigator	Progression-free survival (PFS) is defined as time from first dose of INC280 to progression or death due to any cause PFS per RECIST 1.1, both by BIRC and investigator

	Other secondary endpoint	OS	Overall survival (OS) is defined as time from first dose of INC280 to death due to any cause		
Database lock	11 November 2020				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	FAS: Full analysis set includes all patients who receive at least one dose of INC280				
Descriptive statistics and estimate variability	Treatment group	Cohort 4 (2/3L, MET mutant)	Cohort 6 (2L, MET mutant)	Cohort 5b (1L, MET mutant)	Cohort 7 (1L, MET mutant)
	Number of subjects	69	31	28	32
	ORR by BIRC (%)	40.6%	51.6%	67.9%	65.6%
	95% exact Confidence interval	(28.9,53.1)	(33.1,69.8)	(47.6,84.1)	(46.8,81.4)
Analysis description	**Key secondary endpoint**				
	Median DoR by BIRC (months)	9.72	8.38	12.58	NE
	95% exact Confidence interval	(5.55, 12.98)	(4.17, NE)	(5.55, NE)	(5.52, NE)
Analysis description	**Secondary analysis**				
Descriptive statistics and estimate variability	Treatment group	Cohort 4 (2/3L, MET mutant)	Cohort 6 (2L, MET mutant)	Cohort 5b (1L, MET mutant)	Cohort 7 (1L, MET mutant)
	Number of subjects	69	31	28	32
	ORR by investigator (%) (95% CI)	43.5% (31.6,56.0)	45.2% (27.3,64.0)	60.7% (40.6,78.5)	56.3% (37.7,73.6)
	Median DOR (months) by investigator (95% CI)	8.31 (5.45, 12.06)	8.38 (4.17, NE)	13.83 (4.27, 25.33)	9.46 (5.55, NE)
	Median TTR (months) by BIRC (95% CI)	NE (2.76, NE)	9.66 (1.51, NE)	2.69 (1.38, 6.90)	2.79 (1.45, 7.20)

	Median TTR (months) by investigator (95% CI)	NE (1.41, NE)	NE (1.51, NE)	2.69 (1.38, NE)	3.06 (1.45, NE)
	DCR by BIRC (%) (95% CI)	78.3% (66.7,87.3)	90.3% (74.2,98.0)	96.4% (81.7,99.9)	100.0% (89.1,100.0)
	DCR by investigator (%) (95% CI)	76.8% (65.1,86.1)	90.3% (74.2,98.0)	96.4% (81.7,99.9)	96.9% (83.8,99.9)
	Median PFS (months) by BIRC (95% CI)	5.42 (4.17, 6.97)	6.93 (4.17, 13.34)	12.42 (8.21, 23.39)	10.84 (6.87, NE)
	Median PFS (months) by investigator (95% CI)	4.80 (4.11, 7.75)	6.90 (5.55, NE)	11.99 (5.52, 16.92)	9.79 (5.75, 11.89)
	Median OS (months) (95% CI)	13.57 (8.61, 22.24)	NE (13.54, NE)	20.76 (12.42, NE)	NE (10.55, NE)

2.6.3.3. Clinical studies in special populations

Table 47. Overview of patients included in controlled and uncontrolled studies by age group

	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	0	0	0
Non Controlled trials Total Cohorts 4, 5b, 6, 7	 157/373 82/160	 60/373 47/160	 9/373 7/160

There are no dedicated studies for the elderly population, but a high portion of the patients included in the registrational study are older than 65 years (60.6%, 226/373). For the study population of the main 4 cohorts supporting this application, patients with MET mutations, elderly patients represent 85% (136/160) of the actual study population, with 54/160 (33.8%) being 75 years or older. This is considered a fair representation of the elderly population.

No dose adjustments in special populations are warranted.

2.6.3.4. In vitro biomarker test for patient selection for efficacy

In Study A2201, a Novartis-designated central laboratory was used to prospectively confirm the presence of METex14 mutations or MET amplifications. The detection of the METex14 deletion (resulting from exon 14 skipping mutation) was performed using a Novartis-developed RT-PCR clinical trial assay (CTA), which was a qualitative RT-PCR test designed to detect exon 14 deleted MET mRNA derived from formalin-fixed, paraffin-embedded (FFPE) human tissue.

The detection of MET amplification in NSCLC specimens was performed via the Abbott Molecular Inc. Vysis MET FISH kit test, a semi-quantitative test designed to detect the copy number of the MET gene and the copy number of the chromosome 7 centromere in FFPE tissue specimens.

Both RT-PCR and FISH tests were performed in parallel to determine the assignment to each cohort where the presence of MET exon 14 skipping mutations, irrespective of the MET GCN, led to the recruitment into the MET-mutated cohorts. This information is reflected in the SmPc.

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

Not applicable

2.6.3.6. Supportive studies

Study X2401

Study X2401 is a retrospective chart collection to gather RWE data aimed at describing the natural history (including patient and disease characteristics, treatment patterns, and clinical outcomes) of subjects with advanced NSCLC harbouring MET dysregulation treated in clinical practice.

Charts were collected from subjects with advanced MET dysregulated (either mutated or amplified) NSCLC identified in five institutions in USA, 2 institutions in France, 1 in Germany, 2 institutions in Korea, and 1 institution in Japan. A total of 211 charts were collected, out of which 157 were collected from subjects with MET-mutated NSCLC.

Data collection commenced in December 2017 and concluded in September 2018, with study index dates ranging from 2008 to 2018. The date of first diagnosis of or progression to advanced/metastatic stage disease defines the study index date. To allow for an adequate potential follow-up duration (retrospectively observed) after the index date over which treatment patterns and outcomes could be documented, a minimum post-index follow up of at least 12 months was required. Patients with post-index follow up of less than 12 months were eligible for selection if progression had occurred on at least one prior line of systemic therapy in the advanced/metastatic setting or if death occurred in less than 12 months after the index date.

The study included subjects aged 18 years or older with a confirmed diagnosis of advanced/metastatic (stage IIIb not amenable for definitive chemoradiotherapy/stage IV) EGFR wt NSCLC and MET mutation (defined as MET exon 14 skipping mutation) or MET amplification (defined as GCN ≥ 6 or gene ratio ≥ 2.2).

The number of subjects treated with MET inhibitors was restricted to account for no more than 50% of all medical records collected in this study. No subjects treated with capmatinib were included in this chart collection. As MET inhibitors were not approved in this setting of METdysregulated NSCLC back then, subjects included in this chart review received such treatment off-label or in clinical studies.

Results

The main findings in terms of patient and disease characteristics in the MET-mutated NSCLC patients were as follows:

- Consistent with prior reports (Awad et al 2019), MET-mutated NSCLC is diagnosed in older subjects (median age 73 years) [Study X2401-Table 2] compared to unselected NSCLC subjects (median age ~60 years) (Chen et al 2019)
- No substantial difference in gender distribution was observed
- MET-mutated NSCLC seems to occur irrespective of the smoking history and tumour histology
- One-third of the subjects presented with brain metastases and almost two-thirds had bone metastases at the time of initial diagnosis, 17.6% of the subjects had liver metastases at the time of initial diagnosis.
- MET mutation is confirmed to be mutually exclusive from other established molecular drivers tested (ROS1, EML-4-ALK, HER2 exon 20 insertion) while co-occurrence with KRAS mutation was reported in 11 subjects (reflecting 8.1% of those tested for KRAS). Among BRAF-tested cases, 3 subjects (2.3%) were found to be BRAF positive. Among cases tested for PD-L1 (n=90), PD-L1 expression ≥1% was present in a majority of patients (66.7%) and did not vary greatly by mutational status, with more than half of the positive cases (55.6%) showing a PD-L1 expression level of ≥50% [Study X2401].

-Most patients (138 [87.9%]) received at least one line of cancer-directed systemic therapy in the advanced/metastatic setting (Table 6). Nineteen patients received no systemic treatment for advanced stage disease. Approximately half (77 [49.0%]) of all patients received multiple lines;

-As expected, platinum-based chemotherapy was the prevailing first-line treatment regimen in the advanced/metastatic setting; among the 105 patients receiving either platinum- or non-platinum chemotherapy in first-line, 16 (11.6%) received single-agent therapy. later-line regimens were more varied in composition. In total, 49 patients (31.2%) received METi in at least one treatment line

Table 48. Anticancer treatments received in the advanced/metastatic setting

	All MET Mutated Patients	
Total Patients, n (%)	157	100.0%
Number of Systemic Treatment Regimens/Therapy Lines Received[a]		
Mean (SD)	1.9	1.5
Median	1	
Min, Max	(0, 7)	
Distribution, n (%)		
0 (no cancer-directed systemic treatment initiated)[b]	19	12.1%
1	61	38.9%
2	36	22.9%
3	18	11.5%
≥4	23	14.7%
Number of Lines of METi Therapy Received, n (%)[a]		
None	108	68.8%
1 line	37	23.6%
2 lines	12	7.6%
Received I/O Therapy in Any Treatment Line, n (%)[a]		
No	109	69.4%
Yes	48	30.6%

[a] After first diagnosis of (or progression to) advanced/metastatic disease (index date).
[b] 15 of the 19 patients who did not receive systemic treatment died before a first-line treatment could be initiated.
SD = standard deviation, NSCLC = non-small cell lung cancer, I/O = immuno-oncology (defined as treatment with nivolumab, pembrolizumab, avelumab, atezolizumab, or durvalumab)

The main findings describing the prognostic and predictive role of MET mutation are as follows:

In terms of survival duration, which remains the most reliable and unbiased endpoint in such type of retrospective chart collection, results indicate that the median OS for subjects with MET-mutated NSCLC

receiving standard therapies (i.e. subjects who did not receive MET inhibitor therapy in any treatment line) was considerably shorter than the median OS reported for historical controls in unselected advanced NSCLC (Paz-Ares et al 2013, Scagliotti et al 2014, Reck et al 2016, Carbone et al 2017, Gandhi et al 2018, Socinski et al 2018, Xia et al 2019).

The survival benefit seems to be improved when treated off label with a MET inhibitor:

- Median OS since diagnosis of advanced stage was 25.4 months (n = 49, 95% CI: 18.8, 40.9) in MET inhibitor treated versus 10.7 months (n = 108, 95% CI: 7.8, 14.4) in MET inhibitor non-treated subjects [Study X2401-Table 7].

Table 49. Kaplan-Meier estimates of overall survival from first diagnosis of advanced/metastatic NSCLC, by METi treatment status

	Received METi[a] (n = 49)	Did Not Receive METi[a] (n = 108)
N (%) of patients with event	27 (55.1%)	72 (66.7%)
Median, months (95% CI)	25.4 (18.8, 40.9)	10.7 (7.8, 14.4)
6-Month OS Rate	91.8%	65.4%
12-Month OS Rate	78.7%	46.4%

[a] Receipt of METi defined by treatment with a METi at any point after first diagnosis of (or progression to) advanced/metastatic disease; METi class includes: cabozantinib, crizotinib, emibetuzumab, ficlatuzumab, foretinib, glesatinib, merestinib, onartuzumab, rilotumumab, SAR125844, sitravatinib, tepotinib, tivantinib.
NSCLC = non-small cell lung cancer, CI = confidence interval, OS = overall survival, METi = MET inhibitor

- For first-line platinum recipients with MET mutation who did not receive METi therapy in any line, median (95% CI) OS from first-line treatment initiation was 9.1 (7.5, 18.9) months, with 6- and 12-month OS rates of 68.9% and 41.0%, respectively. Median OS was 18.4 months (n = 12, 95% CI: 1.5, 18.4) in first-line IO-based treatment in subjects who did not receive any MET inhibitors and was 11.9 months (n = 9, 95% CI: 2.1, NE) in subjects who received IO as second- or third-line treatment. The median OS for subjects who received single-agent chemotherapy as second- or third-line treatment was 13.2 months (n= 16, 95% CI: 3.0, 42.7) [Study X2401-Table 8].

Table 50. Kaplan-Meier estimates of overall survival, by selected treatment groups for patients who did not receive METi in any treatment line

	1L Platinum-Based Treatment Recipients (n = 61)	1L I/O Recipients[a] (n = 12)	2L/3L I/O Recipients[a] (n = 9)	2L/3L Single-Agent Chemo Recipients (n = 16)
	(from 1L initiation)	(from 1L initiation)	(from 2L/3L initiation)[b]	(from 2L/3L initiation)[b]
N (%) of patients with event	43 (70.5%)	5 (41.7%)	4 (44.4%)	7 (43.8%)
Median, months (95% CI)	9.1 (7.5, 18.9)	18.4 (1.5, 18.4)	11.9 (2.1, NE)	13.2 (3.0, 42.7)
6-Month OS Rate	68.9%	75.0%	76.5%	63.0%
12-Month OS Rate	41.0%	64.3%	42.5%	63.0%

[a] I/O class includes nivolumab, pembrolizumab, avelumab, atezolizumab, durvalumab.
[b] Estimated from 2L or 3L initiation, depending on the line in which I/O or single agent chemo was first received.
NSCLC = non-small cell lung cancer, CI = confidence interval, I/O = immune-oncology, NE = not estimable, 1L = first-line, 2L = second-line, 3L = third-line

- For first-line platinum recipients, median (95% CI) PFS from first-line treatment initiation for advanced or metastatic disease was 5.1 (3.3, 6.9) months. The median PFS for all subjects included who received IO-based therapy as first-line treatment was 2.6 months (n = 17, 95% CI: 1.0, 6.9). The median PFS for subjects who received IO as second or third-line treatment was 3.1 months (n = 24, 95% CI: 1.9, 4.1). The median PFS for subjects who received single-agent chemotherapy as

second- or third-line treatment was 2.8 months (n= 22, 95% CI: 1.2, 5.0).

It is noted that these are highly selected centres, given the non-spread access to METmut diagnosis and to the most innovative treatment options, including medicinal products under investigation like MET inhibitors, for this clinical setting in most European sites. So, treatment outcomes might have been overestimated. This should be born in mind when interpreting the data.

Results should be interpreted with caution and formal comparisons with other cohorts of patients, including those receiving METi vs non-METi within the same METmut retrospective cohort, cannot be done reliably as there may well be underlying differences in demographics/disease characteristics/unknown risk factors determining differential prognosis. Indeed, these differences might well explain the decision to consider an additional line of therapy with a medicinal product under investigation like MET inhibitors in the current cohort for a small/selected subset of METmut patients. This limitation precludes a definitive answer to establish if the presence of MET mutations is a marker per se of poor prognosis in subjects with NSCLS, and/or a predictive factor of poor response to SOC therapies, as it is claimed. Nevertheless, it is recognised that taking together all the available evidence it can reasonably be ruled out just the opposite, i.e. that the presence of MET mutations in patients with NSCLC determines a good prognosis and/or a better response to SOC therapies. Indeed, all the evidence points into the opposite direction, but a definitive conclusion cannot be drawn given the quality of the evidence available.

Study A2405

Study A2405 was a retrospective secondary use of data analysis to contextually understand the baseline characteristics, treatment patterns, and clinical outcomes of real-world advanced NSCLC patients with MET exon 14 mutation tumours from the Flatiron Health CGDB, originally intended to explore the use of an external real-world control for single-arm Study A2201. The real-world descriptive cohorts were established from a well-documented population of patients observed between January 2011 and December 2019 through EHRs ascertainment in the Flatiron Health network. This Flatiron network has a wide geographic breadth of over 280 US sites, predominantly community oncology practices, with a small number of academic medical centres also available. This network is then paired with genomic data from Foundation Medicine, Inc to provide a combined clinicogenomic database.

The results from the RW-MET-mut populations were compared indirectly to the following two sets of descriptive cohorts:

- Cohorts 4 (pre-treated) and 5b (treatment-naïve) from Study A2201 (DCO 28-Oct-2019)
- Real-world matched cohorts of MET-WT patients from the CGDB.

Baseline criteria were applied to the individual patient-level data from the CGDB to select the real-world cohorts, e.g. patients were required to have at least 1 NGS test. Specific inclusion and exclusion criteria were then applied to match important criteria from Study A2201.

Propensity score weighting (PSW) was implemented to mitigate potential biases related to the external comparator, which primarily accounts for differences in observed baseline patient characteristics between those in Study A2201 and those in the comparator population when estimating the effect of treatment on outcomes. A Kaplan-Meier analysis was conducted to estimate the OS and PFS for each of the comparisons of interest.

Results

External control cohorts consisted of:

- Pre-treated: RW-MET-mut (n=20)
- Treatment-naïve: RW-MET-mut (n=41)

Internal control cohorts consisted of:

- Pre-treated: RW-MET-mut (n=20)
- Treatment-naïve: RW-MET-mut (n=54), and
- Pre-treated: RW-MET-WT (wild type) (n=1222)
- Treatment-naïve: RW-MET-WT (wild type) (n=2010)

This study was initially planned to generate an external cohort of patients to allow comparison with cohorts 4 and 5b of the registrational A2201 study. A numerically longer median PFS and OS were observed among the Trial Cohort as compared to the Real-world Cohort pre- and post-weighting in 1L than 2L setting. However, as already noted by the applicant, the study results show some inconsistencies which can be explained by the existence of important limitations that preclude its use as an external control cohort.

Among the identified limitations: sample sizes of the individual cohorts used to conduct the planned analyses were too small (20 pre-treated and 41 post-treated patients in RW Cohorts, not making possible to apply the propensity score to the pre-treated setting); efficacy assessments in "real world setting" are not systematically conducted at pre-specified times, nor is it common practice to use RECIST 1.1 algorithms; post treatment assignment of cohorts (time zero handling) due to application of NGS results for individual patient records to be included may have introduced bias; over the timespan of database examined in this study (from January 2011 - December 2019), both the treatment landscape and biomarker testing landscape changed extensively; approximately 30% of subjects in real-world MET-mut cohorts received MET inhibitor or clinical study drug during follow-up, confounding comparisons and impacting outcomes, as well as unobserved confounding factors that may still exist when implementing the PSW method (i.e. that only data available in the CGDB can be matched/weighted and there may be missing variables, e.g. ECOG performance status, staging/disease burden).

In conclusion, this study does not provide valuable insight concerning the contextualization of the results.

2.6.4. Discussion on clinical efficacy

The initially sought indication was:

"Tabrecta is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation."

During the procedure, the applicant restricted the indication as proposed by the CHMP:

"Tabrecta as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy"

Design and conduct of clinical studies

The pivotal registration **Study CINC280A2201 (also called GEOMETRY mono-1)** is a global, prospective, multi-cohort, non-randomized, open-label Phase II study with a Bayesian interim monitoring designed to evaluate the efficacy and safety of single-agent capmatinib 400mg bid in subjects with EGFR wild type (wt), ALK negative rearrangement, advanced (stage IIIB or IV) NSCLC harbouring MET mutations (detected by RT-PCR), and/or MET amplification (detected by FISH).

The pivotal trial supporting this application is a single-arm phase II trial. Generally, a confirmatory comparative phase III study is preferred as registration study. The applicant sought regulatory input via national and CHMP scientific advice. The CHMP advised that the option to conduct a (small) RCT could be explored and informed the applicant on the risk of not providing robust data with a single-arm trial. Not initiating an RCT in the first-line setting is considered a missed opportunity.

Primary efficacy data supporting the indication are restricted to 4 cohorts that include previously treated NSCLC patients with METex14 skipping mutations (Cohorts 4 and 6, n=100) and treatment-naïve NSCLC patients with METex14 skipping mutations (Cohorts 5b and 7, n=60). Expansion Cohorts 6 and 7 were added to generate additional supportive safety and efficacy data by means of replication in the pre-treated and treatment-naïve settings, respectively, in consideration of feedback from health authority (HA) consultations.

The detection of the METex14 deletion (resulting from exon 14 skipping mutation) was performed using a RT-PCR clinical trial assay (CTA) developed by the applicant, which was a qualitative RT-PCR test designed to detect exon 14 deleted MET mRNA derived from formalin-fixed, paraffin-embedded (FFPE) human tissue. The applicant provided additional information regarding the accuracy and sensitivity of the MET Exon 14 Deletion Test clinical trial assay (CTA). A validation report of the reverse transcriptase-polymerase chain reaction (RT-PCR) that was used in Study A2201 was included. The validation included six studies, addressing limit of blank, limit of detection, precision/reproducibility, interference with necrotic tissue and external factors, analytical specificity and method comparison. Acceptance criteria were determined beforehand. These criteria are appropriate for the detection of METex14 status using RNA isolated from formalin-fixed paraffin embedded sections. All criteria were successfully met. When detecting the presence of alterations leading to METex14 skipping using tissue-based or plasma-based specimens, it is important that a well-validated and robust test is chosen to avoid false negative or false positive results.

The primary objective is to evaluate the antitumour activity of capmatinib, as measured by overall response rate (ORR) by BIRC assessment, by cohort; ORR defined as the proportion of subjects with a best overall response (BOR) defined as complete response or partial response (CR+PR) per RECIST version 1.1. Secondary endpoints include DOR by BIRC, ORR and DOR per RECIST 1.1 by investigator assessment, time to response (TTR), DCR, PFS, and OS.

The study design, objectives, and efficacy endpoints are clearly defined, and are in line with exploratory studies. However, the lack of randomisation and the open-label design mean that a risk for both selection and assessment bias cannot be totally ruled out, which is of importance considering that this study is the registrational or pivotal evidence supporting the claimed indication and what should be considered when interpreting the data. An independent central review committee for antitumor assessment and determination of METex14 status by a central laboratory were put in place, which reduce the risk of bias. However, an overestimation of the antitumor effect by the selection of a favourable subset of METmut patient by the investigators and/or by the assessment of tumour responses cannot be completely ruled out. Furthermore, the lack of control arm poses an additional challenge to the interpretation of the clinical relevance of the study results and to the estimation of the actual benefit on relevant clinical outcomes.

Furthermore, the primary objective of study A2201 was to demonstrate anti-cancer activity and the corresponding primary endpoint was overall response rate (ORR). This endpoint is an interpretable endpoint for single-arms trials and may predict clinical benefit. Spontaneous regression of the tumour, at least to an extent that fulfils the criteria of partial response or better, is not common (EMA anti-cancer guideline 2017). Responses were assessed per BIRC, which provides a less biased assessment of the responses, i.e. preventing potential assessment bias. Encouraging anti-tumour activity has translated into survival benefits for other targeted therapies in advanced NSCLC (e.g. ALK inhibitors), however ORR is not considered an adequate surrogate for overall survival.

The censoring rules for DOR may lead to informative censoring as well as a potentially inflated treatment effect given the rules that patients who discontinue treatment due to clinical progression and/or receive new anticancer therapy before a progression were to be followed up under a treatment policy estimand strategy.

Treatment with capmatinib could continue beyond disease progression if there was evidence of clinical benefit based on the Investigator's judgment, and if the subject wished to continue on study treatment.

Supportive evidence is limited to the results of a dose-finding study conducted in different tumour types, which includes results for only 4 METexon 14 skipping mutated NSCLC patients and overall provides support for the dose tested in the phase II. Retrospective data from two different cohorts are presented with the aim to provide some insight on the natural history of the disease in METexon 14 skipping mutated NSCLC patients (Study X2401) and to contextualise the uncontrolled results by introducing a comparison to real-world data (Study A2405). The applicant was advised by SAWP (EMEA/H/SA/2973/2/2019/II) that the proposed contextualisation to RWD could be considered supportive at best, as it cannot compensate for the fundamental methodological deficiencies of the proposed package intended for the primary efficacy demonstration. So, the registrational Study GEOMETRY mono-1 is the main, and nearly the only, evidence provided in support of a line agnostic indication for patients with METexon 14 skipping mutated NSCLC. This *a priori* raises serious concerns in view of the existing uncertainties on the actual prognostic/predictive value of this marker, the inherent difficulties in interpreting SATs in this context, and also considering that well-established SOC therapies exist for these patients.

No inferential analyses were planned for this study as this was formally a non-comparative study of several cohorts of patients treated with capmatinib. The initially targeted sample size was 69 subjects for Cohorts 1a, 1b, 2, 3, and 4, 27 subjects per cohort in Cohorts 5a and 5b, approximately 30 subjects in Cohort 6 and approximately 27 subjects in Cohort 7, if none of the Cohorts 1-4 was stopped for futility at the time of the interim analysis. The aim was to show an ORR with the lower bound of the 95% confident limit above that considered clinically relevant for the two main clinical settings, i.e. 35% for treatment naïve, and 25% for the pre-treated cohorts. Interim analysis for futility were planned in the study protocol for Cohorts 1a, 1b, 2, 3, and 4, with clearly established stopping criteria (POS <10%).

The primary analysis was performed per cohort, and, as outlined above, different hypotheses were to be tested depending on whether patients were pre-treated or treatment-naïve. The thresholds for the ORR to be considered as clinically relevant were based on historical data. However, more recently, the treatment landscape in first- and subsequent lines is reshaped due to the approval of immunotherapy, with higher reported ORR rates in the first line setting.

For the second and third-line setting, the lower bound can still be considered clinically relevant; particularly for patients that are no longer candidates for second-line immunotherapy. It should be noted that patients with advanced non-squamous NSCLC treated with docetaxel had a ORR of 12% (Borghaei et al. NEJM 2015).

For the first-line treatment setting, the relevance of the selected lower bound of the CI can be questioned due to the more recent addition of immunotherapy to platinum-based chemotherapy. For example, ORR was 47.6% for pembrolizumab in combination with platinum-based chemotherapy (Gandhi et al NEJM 2018). Therefore, even though efficacy might be concluded on the basis of these criteria for the first-line cohorts (i.e. cohort 5b and 7), a discussion on the clinical relevance of the outcome is still considered necessary taking into account the current treatment landscape and the fact that current available treatments in the first line have shown a survival benefit compared to SoC.

The primary analysis was performed on the **full analysis set (FAS),** which includes all patients who received at least one dose of capmatinib and was conducted when all treated patients in cohorts that are not stopped for futility (at the time of the interim analysis) have completed at least 6 cycles of treatment (18 weeks) unless a patient has discontinued treatment earlier.

The amendments have been justified satisfactorily and did not impact the assessment of the study results.

Across all cohorts (i.e. cohorts 1-7), protocol deviations were commonly observed. However, only the minority of these deviations led to exclusion from the per protocol set, indicating that most of the deviations were minor and did not have an impact on the interpretation of the efficacy results.

Efficacy data and additional analyses

Overall, 472 subjects signed the main study informed consent, among whom 373 subjects (79.0%) completed the screening phase and had at least one dose of study treatment. The enrolment is closed for all cohorts. Enrolment in Cohorts 1b, 2, and 3 was stopped for futility. The study is ongoing.

Screen failure was the predominant reason for not completing the screening phase. The most frequently reported unmet criteria were adequate organ function at screening (38.4%, ECOG score > 1 (17.4%), and assignment to one of the other cohorts according to MET mutations, MET dysregulation criteria (n=18.7%). Only one patient assigned to another cohort harboured a METex14 skipping alteration as defined by central testing, but was later considered a screening failure by the investigator.

The clinical efficacy evidence in this MAA focuses on cohorts with MET-mutated subjects with **DCO 18-Sep-2020**: at the time of this DCO 33 out of 160 subjects (20.6%) included in any of the four key cohorts (C4, C5b, C6, C7) for this application are still on treatment. The main reasons for treatment discontinuation, consistent in each cohort, were disease progression (80/127, 50%) and adverse events (28/127, 17.5%).

Demographic and Disease Characteristics

In general, demographic and disease characteristics were representative of the population of adult subjects with EGFR wt advanced NSCLC. Subjects with MET-mutated NSCLC were older (median age: 71 years, 33.7% patients older than 75 years, 85% older than 65 years)) than non-MET mutated subjects, 60.6% females and never-smokers. The study included patients with an ECOG PS of 0 (25.0%) and 1 (74.4%). Adenocarcinoma was reported as the primary histology (82.5%). The pre-treated subjects showed greater disease extent than the treatment-naïve subjects.

Of the 100 MET-mutated subjects in the 2nd/3rd line pre-treated setting (Cohorts 4 and 6), 81 subjects (81.0%) received one prior line of systemic therapy-medication for advanced disease, 16 subjects (16.0%) had received two prior lines, and 3 subjects (3.0%) had received 3 prior lines before receiving capmatinib. The majority of subjects (86.0%) received platinum-based chemotherapy prior to entering the study (irrespective of the line). The use of immunotherapy regardless of line of treatment was 41.9% in Cohort 6 vs 27.5% in Cohort 4. Reported best ORR to prior therapy was 10.1% for Cohort 4 and 16.1% for Cohort 6, all being partial responses, which is lower than that reported with SOC in first line, and even for second line, in the general NSCLC population and consistent with evidence that support lower treatment outcomes in this subset of patients.

It is however questioned whether the results on prior therapy – at least as currently presented – are informative. The limited sample size as well as different types of therapies makes it challenging to determine how patients responded to prior systemic therapy such as chemotherapy and/or immunotherapy. Moreover, for 36% subjects 'not applicable' was reported as best response to last therapy ("Best response at last therapy will be set to 'Not applicable' if the type of last therapy is surgery or radiotherapy."). Hence, it is not clear whether these patients respond to prior systemic

therapy. As a result, it is unlikely that the percentages mentioned above are representative for the overall population.

As of the DCO of 18-Sep-2020, of the 100 MET-mutated subjects in Cohorts 4 and Cohort 6, the majority (74/100, 74.0%) received chemotherapy as the last systemic therapy prior to entering the study, 25% (25/100) received immunotherapy and 1% (1/100) received targeted therapy as the last systemic therapy prior to entering the study. The best response to last therapy reported (≥10% subjects) was 36% of progressive disease, 28% of stable disease and 21% of partial response. Best response of complete response was not reported. The overall tumour responses appear lower than those commonly reported by available SOC but given that this is a limited and selected population this data should be interpreted with caution.

Brain metastases are reported in 20- 40% of NSCLC patients harbouring METex14 skipping alterations. The presence of brain metastases is an extremely poor prognostic factor with a median survival without treatment of 1-2 months, and 4-7 months survival with treatment, respectively. A lower rate of brain metastasis than that reported in published series (20-40%) is described for patients included in any of the capmatinib Cohorts 4, 5b, 6 and 7 (15-17%), limiting the ability to reach sound conclusions on the effect on brain metastases in these patients.

Overall, the baseline demographics and characteristics were generally in line with results from literature (Vuong et al. Lung cancer 2018, Digumarthy et al. Cancers 2019), indicating that the study population sufficiently reflects the target population. The median age of patients in study A2201 was however slightly lower than that of patients included in another study investigating a MET inhibitor (71 years vs 74 years; Paik et al. NEJM 2020), but still higher that usually reported in clinical trials that include patients with advanced NSCLC. The number of patients with brain metastases appears to be lower than reported in other studies (Awad et al. Lung Cancer. 2019), but since eligibility was limited to patients with stable CNS metastases this is understood. Other noticeable differences between the study and the target population are those often seen in a clinical trial setting, such as the exclusion of patients with poorer performance status or inadequate organ function

Efficacy results (DCO 18 September 2020)

For the population harbouring METex14 skipping alterations, the primary efficacy results were presented after a median study follow-up of 34.0 months (range: 27.5 to 42.0) and 10.0 months (range: 6.3 to 15.2) for Cohorts 5b and 7, respectively; and 39.7 months (range: 29.5 to 53.3) and 19.5 months (range: 15.7 to 26.7) for Cohorts 4 and 6, respectively.

The observed overall tumour response rate was 44.0% (pooled Cohort 4 and 6, n=100) in the previously treated patients, with a reported mDoR of 9.72 months. For the treatment naïve patients, the reported ORR was about 66.7% (pooled cohorts 5b and 7), with a reported mDoR of 12.58 months.

During the procedure updated efficacy results were provided (latest information corresponding to a DCO of 30 August 2021). The updated results confirmed the initial analyses for the pre-treated cohorts 4 and 6 pooled (ORR 44%, mDoR 9.72 months), and the naïve cohorts 5b and 7 pooled (ORR 68.3%, mDoR 16.59 months).

The requested additional sensitivity analyses were provided for the handling of the events 'Adequate assessment no longer available' and 'Event after ≥ 2 missing assessments'. For the estimation of DoR in cohorts 4 and 6, the number of censored patients was small and as a result the DoR in the 2/3L cohorts was consistent with the primary analysis results when these subjects were considered to have had an event.

For the treatment naïve cohorts, cohort 5 and 7, the DoR was more sensitive to the handling the events 'Adequate assessment no longer available' and 'Event after ≥ 2 missing assessments'. If these

were considered events then the median DoR in the pooled cohorts reduced to 12.58 [95% CI: 7.75, 19.35] compared with 16.59 [95% CI: 8.41, 22.11] months in the primary analysis. This data show that the DoR in the treatment naive population is sensitive to how the missing data is handled.

Overall, high tumour responses rates and durable responses as assessed by BIRC are observed across all four Cohorts, including treatment naïve and pre-treated subjects. The majority of the evaluable subjects in Cohorts 5b (96.2%) and 4 (90.0%), and all subjects in Cohorts 6 and 7 showed tumour shrinkage. Consistent results were observed in the sensitivity analyses conducted, and also for the subgroups analysed, according to age, gender, ECOG PS 0-1, and by race. Results in Cohorts 4 and 5b were replicated in their respective expansion cohorts 6 and 7. All these analyses add robustness to the estimation of the antitumoral activity of capmatinib.

This internal replication, together with the biological plausibility add to the credibility of the results. Moreover, there is emerging evidence on the relevance of MET inhibition in this target population (e.g. tepotinib, crizotinib), which further supports the opinion that MET-inhibitors are valuable treatment options for patients with NSCLC with a METex14 skipping mutation.

ORR was numerically lower in pre-treated patients compared to treatment-naïve patients. The applicant mentions that this resembles a similar differential effect shown with other targeted therapies for established molecular drivers, where the efficacy (mainly ORR) shows a trend in declining response rates from treatment-naïve to subsequent lines of therapy (Shaw et al 2013, Solomon et al 2014, Mok et al 2017, Soria et al 2018). However, differences in ORR between treatment-naïve and pre-treated patients were not evident for other MET inhibitors such as crizotinib (Socinski et al. JCO Precision Oncology. 2021, Paik et al. NEJM. 2020). When discussing the results of capmatinib, Wolf et al. state that "An overall decline in health during longer durations of disease, as well as the evolution of resistant clones during first-line therapy, might contribute to this observation" (Wolf et al. NEJM 2020).

The concordance rate between investigator-assessed ORR and BIRC-assessed ORR was sufficiently high. For cohort 4 and 5b, ORR results for the per-protocol set (PPS) and FAS were consistent.

The treatment effect was generally consistent across subgroups and confidence intervals were overlapping. For cohort 5b, 6 and 7, a few subgroups showed a smaller treatment-effect than observed for the overall cohorts, but these subgroups consisted of only a few patients resulting in imprecise estimates. This heterogeneity can be expected and is not alarming.

Capmatinib can cross the blood-brain barrier. Sixteen (16) out of 29 patients who had brain lesions showed intracranial lesion shrinkage, based on a post-hoc analysis. Of these 16 patients, 6 received intracranial radiation before study entry, which can be considered a confounding factor. Nonetheless, these data are indicative of intracranial activity, at least in patients with stable CNS metastases.

The majority of responses were observed within two months and responses were relatively durable, The mDoR was numerically longer in the first-line setting compared to the second or later-line setting (12.58 and 16.59 months in Cohort 5b and 7, respectively, vs 9.05-9.72 months in Cohort 6 and 4, respectively).

The censoring rules for DOR (see Table 27 in the clinical efficacy section) may lead to informative censoring as well as a potentially inflated treatment effect given the rules that patients who discontinue treatment due to clinical progression and/or receive new anticancer therapy before a progression were to be continued to be followed up under a treatment policy estimand strategy.

The number of patients who received subsequent therapy is lower in the 1L than second line, which aligns with previous data reported in advanced NSCLC and means that the 1L NSCLC patients have a very bad prognosis. The number of patients that could receive subsequent therapy was about 40-50% in the 1L setting. This pertained to chemotherapy immunotherapy combination, immune-monotherapy,

chemotherapy or other targeted therapy. As is well-known, the patients who survive after 1L therapy and are fit for second line treatment are considered a distinct subgroup, thus it is not surprising that the number of patients who proceed to subsequent therapy after the second line is higher. Nevertheless, no systemic overview of data is provided how long this subsequent antineoplastic treatment was given, which might have provided an indirect measurement of the response to therapy.

The magnitude of the tumour responses are well above the clinically relevant cut-offs as defined in the study protocol, with the lower limit of the 95% confidence intervals above 35% for the treatment naïve patients Cohorts (5b and 7) and above 25% for the pre-treated subjects Cohorts (4 and 6).

METex14 skipping mutations as prognostic factor and response to available therapies

There is evidence suggesting that METex14 skipping mutations are associated with a poor prognosis (Socinski et al. JCO Precision Oncology. 2021; Tong et al. Clinical Cancer Research. 2016), but this is not yet confirmed by available data (Vuong et al. Lung cancer 2018).

The applicant states that clinical benefit with currently approved treatment options is limited in patients with NSCLC harbouring METex14 mutations, and specifically focuses on immunotherapy. Socinski et al. decribed that "The available evidence supporting the use of immunotherapy in patients with METex14 NSCLC is not definitive, and reported response rates are mixed" (Socinski et al. JCO Precision Oncology. 2021). This statement seems fair, since results are inconsistent (Sabari et al. Ann Oncol. 2018; Guisier et al. Journal of Thoracic Oncology 2018). Hence, currently the evidence on this topic is limited but the data at least do not indicate that MET is a predictive marker for improved response to available therapies.

For the pre-treated (2/3L) patient population

Clinical practice guidelines recommend second-line chemotherapy (e.g. docetaxel or pemetrexed) in patients who received prior immunotherapy (Planchard et al. Ann Oncol. 2018). Docetaxel is a commonly used comparator in clinical trials in the second-line setting, for both completed studies (e.g. second-line immunotherapy; NCT01673867, NCT01905657) as well as recently initiated phase III trials (e.g. second-line targeted therapy; NCT04427072, NCT04303780). Albeit an indirect comparison, ORR and DoR with capmatinib compare favourably to ORR and DoR with docetaxel or pemetrexed. For example, in patients with advanced non-squamous treated with docetaxel, ORR was 12% and mDoR was 5.6 months (Borghaei et al. NEJM 2015). Other recommended second-line therapies such as pemetrexed also showed modest anti-tumour activity (i.e. ORR=9.1%, mDoR=4.6 months; Hanna et al. J Clin Oncol. 2004). Second-line immunotherapy (i.e. anti-PD-1/PD-L1 therapy) is expected to be of less relevance now that immunotherapy in combination with chemotherapy is recommended as first-line therapy, and it is difficult to determine how many patients would still be candidate for immunotherapy in the second-line setting.

The magnitude of achieved tumour responses is well above those observed with SOC therapies in second or subsequent lines, as reported for a non-selected NSCLC population (median ORR 9.3% for docetaxel to 18-20% for monotherapy with immunotherapy); though longer duration of responses are normally seen with immunotherapy in this setting. Tumour responses in cohort 4 and 6 are also substantially higher than those reported by the very same patients following prior antineoplastic therapy (ORR with prior antineoplastic therapy was 10.1% for Cohort 4 (51/69 first line therapy) and 16.1% for Cohort 6 (30/31 in first line therapy)). It is remarkable that reported tumour responses with prior therapies are lower than those reported in the general NSCLC with SOC therapies in first line (most patients received treatment in first line), but this comparison should be made with caution as there may well be differences in baseline characteristics and even on the actual treatment received making them non-comparable. The observed antitumoral results are also in line with those reported for targeted therapies for more frequent mutations in NSCLC. The unprecedented tumour responses seen in this advanced pre-treated population, which are substantially higher than those reported with the prior line treatment received and higher than

those expected with 2L/3L SOC for the general NSCLC, are considered clinically relevant and may well translate into benefit in terms of clinical outcomes, though the magnitude cannot be estimated accurately in this uncontrolled study. Taking together all these arguments, the evidence provided support the benefit of capmatinib in 2L or subsequent lines of therapy in patients with a METex14 skipping mutation. The applicant is recommended to submit the final analysis from study CINC280A2201.

The applicant did initiate a phase III RCT in November 2020, and is planned to enrol 90 patients according a 2:1 randomisation. This trial in the second-line setting compares capmatinib versus docetaxel (NCT04427072 - study A2301). Currently, a total of 79 patients have been pre-screened and 18 patients randomised. Full study enrolment is expected in the second half of 2023 and the estimated date for study completion is 3Q 2024. The difficulty for performing a RCT in the 2L setting is acknowledged given the rarity of the mutation, the COVID pandemic, and the competing field with this product and similar ones (e.g. Tepmetko) approved in various regulatory jurisdictions. Nevertheless, the results of this study will provide additional evidence of the benefit of capmatinib in 2nd line. The applicant will provide the final study results from this RCT, when/if available, in the context of a post-approval commitment (recommendation).

For treatment naïve (1L) patients

Clinical practice guidelines recommend platinum-based chemotherapy (with or without immunotherapy) as first-line therapy (Planchard et al. Ann Oncol. 2018). NSCLC patients with a METex14 skipping mutation are often elderly and these patients might not always be candidates for available therapies. However, 81% of the patients in the pre-treated cohorts received platinum based chemotherapy as first-line therapy. Moreover, platinum-based chemotherapy can still be a valid treatment option in elderly patients (Planchard et al. Ann Oncol. 2018). In addition, immunotherapy could be considered according to standard recommendations in elderly patients (Planchard et al. Ann Oncol. 2018). When examining the observational data (e.g. study X2401, study X2405), it seems that the majority of treatment-naïve patients received platinum-based chemotherapy (with or without immunotherapy).

Updated results from DCO August 2021, show consistent encouraging point estimates of antitumor responses and median DoR in the two cohorts of patients treated in first line. However, the data set is limited (28 and 32 patients in cohort 5b and 7, respectively), while the provided data have wide confidence margins (95% CI (47.6 to 84.1) and (50.0 to 83.9) in cohort 5b and 7, respectively). The lower bound of the 95% CI of the DoR showed a limited DoR of 5.55 months in Cohort 5b, while the follow up for the second cohort is too short to confirm the DoR (median follow up 11.1 months, maximum 23 months) and sensitive to the handling of missing data. Consequently, the precision of the observed activity of the drug on the time-dependent endpoints in the 1L population is considered uncertain and it cannot be excluded that capmatinib perfoms worse compared to SoC in these patients.

Therefore, considerable uncertainties remain on whether the reported ORR and DoR will convert into a patient derived benefit in terms of PFS and OS. In view of the clear effect on OS shown by rigorous scientific and regulatory standards for established therapies and the uncertainties on the benefit of capmatinib in the first line setting, a positive B/R cannot be concluded.

The pretreated population and the data obtained from the observational studies show that most METmut patients (>80%) could tolerate the SoC treatment, while in the absence of studies capable of isolating drug effects on PFS and OS, the activity of the drug in terms of ORR/DoR is not sufficiently high to establish the utility of capmatinib for first line use.

The evidence provided doesn't allow CHMP to conclude that the benefit/risk of capmatinib in 1L is positive, i.e. that capmatinib is a suitable 1L treatment option for the MET-mutated NSCLC population given the lack of data from randomised controlled studies over SOC, uncertainties on the actual prognostic/predictive value of this biomarker, and doubts on the actual antitumoral effect of capmatinib

in 1L due to lack of precision in the estimation. The actual benefit of capmatinib on clinically relevant endpoints is uncertain and whether it would perform worse than the SoC in these patients cannot be ruled out.

Measure of health-related quality of life was an exploratory endpoint of Study A2201. However, given the uncertainties associated with these results, they are considered more hypothesis generating than conclusive and are therefore not included in the SmPC.

2.6.5. Conclusions on the clinical efficacy

For the second- and subsequent line setting, improved efficacy over available therapies is likely, considering that capmatinib shows promising anti-tumour activity that appears sufficient in relation to available therapies. Further, replication of the ORR and DoR data in the 2L+ population has been shown by two independent cohorts and are supported by the DoR and ORR results in the first line setting.

For the first-line setting, it is uncertain whether the reported ORR and DoR will convert to a patient derived benefit like PFS and OS, while established therapies exist with a clear effect on OS shown by rigorous scientific and regulatory standards.

At present, based on the evidence provided a positive benefit/risk can be concluded in the following indication: "Tabrecta as monotherapy is indicated for the treatment of adult patients with advanced non small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum based chemotherapy".

2.6.6. Clinical safety

The safety dataset for this submission includes all available safety data as follows:

- Study A2201: 373 subjects with MET dysregulated NSCLC from the registration study (DCO 18-Sep-2020), including all study cohorts (MET-amplified and MET-mutated) where all subjects received capmatinib at the recommended dose of 400 mg b.i.d. in the tablet formulation. This dataset included 160 MET mutated NSCLC patients (treatment naïve - Cohorts 5b and 7; pre-treated - Cohorts 4 and 6).

- All NSCLC subjects (n = 458): Pooled safety data of capmatinib monotherapy from 6 open-label single-agent studies in subjects with NSCLC: Studies A2201, X1101, X2102, A2103 (only post-DDI phase), A2105 (only post-DDI phase), and A2108.

- All solid tumours subjects (n = 580): Pooled safety data of capmatinib monotherapy from 6 open-label single-agent studies in subjects with advanced solid tumours: Studies A2201, X1101, X2102, A2103 (only post-DDI phase), A2105 (only post-DDI phase), and A2108.

Data from Study X2101T were not pooled with the data from other studies, as the recommended dose was not tested.

The two population subsets from study A2201 ("MET-mutated" and "all subjects" sets) are considered the most relevant for the intended target population. Additional updated data concerning these 2 population subsets were provided during the procedure, with a DCO of 30 Aug 2021. The number of subjects included in this update remained the same (373 "all subjects", 160 "MET-mutated").

2.6.6.1. Patient exposure

Patient disposition

As of the DCO (30-Aug-2021), Study A2201 has completed enrolment for all cohorts and enrolled a total of 373 subjects. At the time of the most recent update, amongst MET mutant subjects, 21 subjects (13.1%) were ongoing in the treatment phase and the primary reasons (> 10%) for discontinuation were disease progression (55.0%) and AEs (20.0%) (Table 51).

Amongst all A2201 subjects, 23 subjects (6.2%) were ongoing in the treatment phase and the primary reasons (> 10%) for discontinuation remained similar to those reported in the original submission, i.e. disease progression (64.1%) and AEs (17.7%).

Table 51. Subject disposition (Full analysis set) – Study A2201

Disposition/Reason	All MET mutant subjects N=160 n (%)	All A2201 subjects N=373 n (%)
Treatment Phase		
Ongoing*	21 (13.1)	23 (6.2)
Discontinued from treatment phase	139 (86.9)	350 (93.8)
Entered post-treatment follow-up	38 (23.8)	95 (25.5)
Entered survival follow-up	74 (46.3)	207 (55.5)
Discontinued from study	27 (16.9)	48 (12.9)
Primary reason for discontinuation from treatment phase		
Adverse event	32 (20.0)	66 (17.7)
Death	1 (0.6)	3 (0.8)
Physician decision	11 (6.9)	25 (6.7)
Progressive disease	88 (55.0)	239 (64.1)
Protocol deviation	0	1 (0.3)
Subject/guardian decision	7 (4.4)	16 (4.3)
Post-treatment follow-up		
Ongoing*	2 (1.3)	3 (0.8)
Discontinued from post-treatment follow-up	36 (22.5)	92 (24.7)
Entered survival follow-up after discontinuation from post-treatment follow-up	22 (13.8)	60 (16.1)
Discontinued from study	14 (8.8)	32 (8.6)
Primary reason for discontinuation from post-treatment follow-up		
Adverse event	2 (1.3)	3 (0.8)
Death	0	1 (0.3)
Lost to follow-up	0	1 (0.3)
Physician decision	6 (3.8)	18 (4.8)
Progressive disease	26 (16.3)	56 (15.0)
Subject/guardian decision	2 (1.3)	13 (3.5)

*Subjects ongoing at the time of the cut-off 30-Aug-2021

Percentages is based on N

Reasons for discontinuation are from "End of treatment Phase Disposition" and "End of Post Treatment Disposition" CRF pages

Extent of the Exposure

Table 52. Duration of exposure to study treatment (Safety set) – Study A2201 (DCO 30 Aug 2021)

	All MET mutant subjects N=160	All A2201 subjects N=373
Total number of subjects receiving study treatment-n (%)	160 (100)	373 (100)
Duration of exposure (weeks)		
Mean (SD)	51.4 (48.93)	36.2 (46.04)
Median	34.9	17.9
Q1-Q3	13.0-78.5	7.0-45.1
Min-Max	0.4-195.7	0.4-281.0
Exposure categories (weeks) -n (%)		
< 6	12 (7.5)	60 (16.1)
6 - <12	18 (11.3)	72 (19.3)
12 - <18	22 (13.8)	55 (14.7)
18 - <24	14 (8.8)	37 (9.9)
24 - <48	31 (19.4)	58 (15.5)
48 - <72	19 (11.9)	35 (9.4)
72 - <84	7 (4.4)	8 (2.1)
84 - <96	6 (3.8)	7 (1.9)
≥96	31 (19.4)	41 (11.0)
Exposure categories -n (%)		
Less than 6 weeks	12 (7.5)	60 (16.1)
At least 6 weeks	148 (92.5)	313 (83.9)
At least 12 weeks	130 (81.3)	241 (64.6)
At least 24 weeks	94 (58.8)	149 (39.9)
At least 48 weeks	63 (39.4)	91 (24.4)
At least 72 weeks	44 (27.5)	56 (15.0)
At least 84 weeks	37 (23.1)	48 (12.9)
At least 96 weeks	31 (19.4)	41 (11.0)
Subject-Months	1890.9	3102.1

Duration of exposure (weeks) = (Last dosing date – First dosing date + 1)/7.
Subject-Months is the sum of each subject's treatment exposure in months.

Table 53. Relative dose intensity of study treatment (Safety set) – Study A2201 – DCO: 30-Aug-2021

	All MET mutant subjects N=160	All A2201 subjects N=373
Total number of subjects receiving study treatment-n (%)	**160 (100)**	**373 (100)**
Relative dose intensity (%)		
Mean (SD)	83.1 (17.85)	85.9 (17.65)
Median	90.4	95.3
(Min-Max)	(38.1-100.0)	(13.0-100.6)
Relative dose intensity categories-n (%)		
≤ 75%	54 (33.7)	99 (26.5)
> 75 to 90%	25 (15.6)	55 (14.7)
> 90 to 110%	81 (50.6)	219 (58.7)

Relative dose intensity include days of zero dose in the calculation.
Relative dose intensity = ((cumulative dose (mg)/duration of exposure)/(planned/cumulative dose (mg)/duration of exposure (days))*100.

Dose reductions and interruptions

Table 54. Dose adjustments of study treatment (Safety set) – Study A2201 – DCO: 30-Aug-2021

	All MET mutant subjects N=160	All A2201 subjects N=373
Dose reduction		
Number of subjects-n (%)		
With no dose reduction	65 (40.6)	193 (51.7)
With at least one dose reduction	95 (59.4)	180 (48.3)
Only one dose reduction	32 (20.0)	74 (19.8)
More than one dose reduction	63 (39.4)	106 (28.4)
Two dose reductions	23 (14.4)	42 (11.3)
More than two dose reductions	40 (25.0)	64 (17.2)
Number of subjects with at least one dose reduction by reason#-n (%)		
Adverse event	73 (76.8)	126 (70.0)
Dosing error	24 (25.3)	52 (28.9)
Subject/guardian decision	22 (23.2)	40 (22.2)
Physician decision	22 (23.2)	37 (20.6)
Technical problems	5 (5.3)	8 (4.4)
Missing	2 (2.1)	2 (1.1)
Dispensing error	1 (1.1)	1 (0.6)
Dose interruption		
Number of subjects-n (%)		
With no dose interruption	53 (33.1)	157 (42.1)
With at least one dose interruption	107 (66.9)	216 (57.9)
Only one dose interruption	37 (23.1)	96 (25.7)
More than one dose interruption	70 (43.8)	120 (32.2)
Two dose interruptions	27 (16.9)	50 (13.4)
More than two dose interruptions	43 (26.9)	70 (18.8)
Number of subjects with at least one dose interruption by reason#-n (%)		
Adverse event	98 (91.6)	195 (90.3)
Physician decision	23 (21.5)	35 (16.2)
Subject/guardian decision	10 (9.3)	22 (10.2)
Dosing error	8 (7.5)	15 (6.9)
Technical problems	0	1 (0.5)
Dispensing error	0	1 (0.5)

Percentage is based on number of subjects with at least one dose reduction or interruption

The median age of subjects was 67.0 years (range: 33.0 to 90.0 years) with 60.6% subjects being ≥ 65 years of age. There was a higher prevalence of male (56.0%) vs. female (44.0%); and 55.0% were ex-smokers. Per protocol, all subjects had ECOG-PS of 0-1 (with the exception of 1 subject with an ECOG-PS 2 at enrolment). The representation of race and ethnicity reflected the countries and regions that participated in the study; the majority of the subjects were Caucasian (75.3%) followed by Asian (22.5%).

In the MET mutant subjects, the median age was 71.0 years. The proportion of subjects in the age group ≥65-<75 years was higher (≥ 5% difference in frequency) in the MET mutant subjects (51.3%) vs all A2201 subjects (42.1%). Similarly, proportion of subjects in the age group ≥75-<85 years was higher in the MET mutant group (29.4%) vs all A2201 subjects (16.1%).
More than half of the subjects in the age group ≥65-<75 years and majority of the subjects in the age group ≥75-<85 years in all A2201 subjects comprised of MET mutant subjects indicating that the older age subgroups in all A2201 subjects were mostly represented by MET mutant subjects (Data not shown).

As pre-defined in the protocol, the majority (98.4%) had Stage IV NSCLC at study entry, which is unsuitable for definitive multimodality therapy and 82.6% subjects had a tumour histology of adenocarcinoma, which is the most commonly occurring histology in subjects with NSCLC. A high proportion (48.0% subjects) had > 3 metastatic sites.

The majority of subjects (89.0%) had received ≥ 1 prior antineoplastic therapy (radiotherapy/surgery/medication). A platinum-based chemotherapy was administered to 74.8% subjects prior to entering the study (irrespective of the line of treatment) and 16.1% subjects received immunotherapies (irrespective of the line of treatment).

Concomitant medications administered during Study A2201 were representative of those routinely prescribed for subjects with locally advanced or metastatic NSCLC, and/or for other illnesses commonly encountered in populations of a similar age. After the study treatment initiation, for concomitant use, 13 (3.5%) subjects took strong CYP3A inhibitors, 1 (0.3%) subject took strong CYP3A inducers, and 116 (31.1%) subjects took medications with a risk of causing QTc prolongation.

2.6.6.2. Adverse events

AEs were coded using MedDRA version 23.1 (original submission) or 24 (update with DCO 30 Aug 2021) and were graded using CTCAE version 4.03.

Table 55. Overview of adverse events categories by grade (Safety set) – Study A2201 – DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
Category	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Adverse events	158 (98.8)	117 (73.1)	367 (98.4)	262 (70.2)
Treatment-related	145 (90.6)	83 (51.9)	324 (86.9)	151 (40.5)
SAEs	79 (49.4)	65 (40.6)	198 (53.1)	162 (43.4)
Treatment-related	26 (16.3)	21 (13.1)	51 (13.7)	36 (9.7)
Fatal SAEs	6 (3.8)	6 (3.8)	12 (3.2)	12 (3.2)
Treatment-related	2 (1.3)	2 (1.3)	4 (1.1)	4 (1.1)
AEs leading to discontinuation	31 (19.4)	22 (13.8)	65 (17.4)	41 (11.0)
Treatment-related	24 (15.0)	16 (10.0)	46 (12.3)	26 (7.0)
AEs leading to dose adjustment/interruption	105 (65.6)	80 (50.0)	230 (61.7)	163 (43.7)
Treatment-related	92 (57.5)	67 (41.9)	179 (48.0)	118 (31.6)
AEs leading to dose adjustment	60 (37.5)	18 (11.3)	98 (26.3)	28 (7.5)
Treatment-related	59 (36.9)	18 (11.3)	95 (25.5)	28 (7.5)
AEs leading to dose interruption	96 (60.0)	71 (44.4)	211 (56.6)	148 (39.7)
Treatment-related	81 (50.6)	57 (35.6)	158 (42.4)	100 (26.8)
AEs requiring additional therapy	145 (90.6)	87 (54.4)	344 (92.2)	202 (54.2)
Treatment-related	113 (70.6)	40 (25.0)	246 (66.0)	74 (19.8)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.

Most frequently reported AEs per SOC are shown in Table 56 for both populations subsets.

Table 56. Adverse events irrespective of study drug relationship by system organ class and maximum grade (Safety set) – Study A2201 – DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
Primary system organ class	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	158 (98.8)	117 (73.1)	367 (98.4)	262 (70.2)
General disorders and administration site conditions	126 (78.8)	44 (27.5)	285 (76.4)	91 (24.4)
Gastrointestinal disorders	111 (69.4)	5 (3.1)	274 (73.5)	31 (8.3)
Investigations	107 (66.9)	43 (26.9)	228 (61.1)	89 (23.9)
Respiratory, thoracic and mediastinal disorders	92 (57.5)	28 (17.5)	202 (54.2)	63 (16.9)
Metabolism and nutrition disorders	76 (47.5)	15 (9.4)	167 (44.8)	38 (10.2)
Musculoskeletal and connective tissue disorders	73 (45.6)	8 (5.0)	153 (41.0)	19 (5.1)
Infections and infestations	59 (36.9)	19 (11.9)	143 (38.3)	46 (12.3)
Nervous system disorders	56 (35.0)	2 (1.3)	116 (31.1)	11 (2.9)
Skin and subcutaneous tissue disorders	53 (33.1)	2 (1.3)	112 (30.0)	5 (1.3)
Psychiatric disorders	41 (25.6)	3 (1.9)	81 (21.7)	6 (1.6)
Blood and lymphatic system disorders	25 (15.6)	6 (3.8)	59 (15.8)	22 (5.9)
Vascular disorders	29 (18.1)	11 (6.9)	59 (15.8)	20 (5.4)
Cardiac disorders	26 (16.3)	4 (2.5)	51 (13.7)	11 (2.9)
Injury, poisoning and procedural complications	32 (20.0)	3 (1.9)	49 (13.1)	6 (1.6)
Ear and labyrinth disorders	25 (15.6)	4 (2.5)	43 (11.5)	5 (1.3)
Eye disorders	19 (11.9)	1 (0.6)	29 (7.8)	2 (0.5)
Renal and urinary disorders	6 (3.8)	0	25 (6.7)	3 (0.8)
Reproductive system and breast disorders	17 (10.6)	2 (1.3)	23 (6.2)	6 (1.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (6.3)	4 (2.5)	21 (5.6)	11 (2.9)
Hepatobiliary disorders	8 (5.0)	3 (1.9)	12 (3.2)	5 (1.3)
Endocrine disorders	4 (2.5)	1 (0.6)	9 (2.4)	2 (0.5)
Immune system disorders	6 (3.8)	0	7 (1.9)	0
Congenital, familial and genetic disorders	1 (0.6)	0	1 (0.3)	0
Product issues	0	0	1 (0.3)	0

Primary system organ classes are sorted in descending frequency of 'All Grades' column, as reported under 'All A2201 subjects'.

A subject with multiple occurrences of an AE under one cohort is counted only once in the AE category for that cohort.

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

The event with maximum severity was counted for subjects who experienced multiple episodes of an event.

Only AEs occurring during on-treatment period were summarized. Missing grades were included under 'All grades' column.

MedDRA version 24.0 was used. AEs were graded according to the CTCAE V4.03.

The most frequently reported AEs by PT, irrespective of study drug relationship (≥ 20% subjects) are shown in Table 57.

Table 57. Adverse events irrespective of study drug relationship by preferred term and maximum grade with an incidence ≥5% (all grades in any population) (Safety set) – Study A2201 – DCO 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)
- Total	158 (98.8)	117 (73.1)	367 (98.4)	262 (70.2)
Oedema peripheral	104 (65.0)	22 (13.8)	203 (54.4)	37 (9.9)
Nausea	71 (44.4)	1 (0.6)	170 (45.6)	9 (2.4)
Vomiting	40 (25.0)	1 (0.6)	106 (28.4)	9 (2.4)
Blood creatinine increased	54 (33.8)	1 (0.6)	101 (27.1)	1 (0.3)
Dyspnoea	36 (22.5)	11 (6.9)	93 (24.9)	26 (7.0)
Fatigue	40 (25.0)	7 (4.4)	86 (23.1)	16 (4.3)
Decreased appetite	34 (21.3)	2 (1.3)	80 (21.4)	4 (1.1)
Constipation	21 (13.1)	2 (1.3)	70 (18.8)	3 (0.8)
Diarrhoea	25 (15.6)	0	69 (18.5)	2 (0.5)
Back pain	33 (20.6)	2 (1.3)	63 (16.9)	3 (0.8)
Cough	28 (17.5)	1 (0.6)	62 (16.6)	2 (0.5)
Alanine aminotransferase increased	23 (14.4)	13 (8.1)	53 (14.2)	26 (7.0)
Pyrexia	17 (10.6)	2 (1.3)	52 (13.9)	3 (0.8)
Asthenia	17 (10.6)	6 (3.8)	47 (12.6)	14 (3.8)
Arthralgia	23 (14.4)	1 (0.6)	46 (12.3)	4 (1.1)
Pneumonia	15 (9.4)	6 (3.8)	42 (11.3)	17 (4.6)
Weight decreased	20 (12.5)	0	41 (11.0)	2 (0.5)
Aspartate aminotransferase increased	13 (8.1)	5 (3.1)	38 (10.2)	13 (3.5)
Hypoalbuminaemia	19 (11.9)	1 (0.6)	38 (10.2)	3 (0.8)
Lipase increased	22 (13.8)	15 (9.4)	37 (9.9)	25 (6.7)
Amylase increased	18 (11.3)	9 (5.6)	36 (9.7)	15 (4.0)
Anaemia	15 (9.4)	4 (2.5)	35 (9.4)	11 (2.9)
Non-cardiac chest pain	9 (5.6)	1 (0.6)	35 (9.4)	4 (1.1)
Pruritus	17 (10.6)	1 (0.6)	35 (9.4)	1 (0.3)
Dizziness	19 (11.9)	0	34 (9.1)	1 (0.3)
Insomnia	20 (12.5)	0	34 (9.1)	0
Headache	14 (8.8)	0	30 (8.0)	1 (0.3)
Pleural effusion	12 (7.5)	2 (1.3)	30 (8.0)	10 (2.7)
Abdominal pain upper	15 (9.4)	0	28 (7.5)	1 (0.3)
Pain in extremity	15 (9.4)	1 (0.6)	28 (7.5)	3 (0.8)
Abdominal pain	11 (6.9)	2 (1.3)	27 (7.2)	7 (1.9)
Dyspepsia	12 (7.5)	0	27 (7.2)	0
Muscle spasms	9 (5.6)	0	26 (7.0)	0
Blood alkaline phosphatase increased	12 (7.5)	1 (0.6)	25 (6.7)	1 (0.3)
Gamma-glutamyltransferase increased	8 (5.0)	4 (2.5)	24 (6.4)	9 (2.4)

Hypokalaemia	10 (6.3)	1 (0.6)	24 (6.4)	5 (1.3)
Rash	13 (8.1)	0	24 (6.4)	1 (0.3)
Nasopharyngitis	9 (5.6)	0	23 (6.2)	0
Hypocalcaemia	19 (11.9)	0	22 (5.9)	0
Weight increased	11 (6.9)	2 (1.3)	21 (5.6)	2 (0.5)
Hypophosphataemia	10 (6.3)	6 (3.8)	20 (5.4)	9 (2.4)
Musculoskeletal chest pain	9 (5.6)	1 (0.6)	20 (5.4)	3 (0.8)
Pulmonary embolism	6 (3.8)	3 (1.9)	20 (5.4)	12 (3.2)
Dry skin	4 (2.5)	0	19 (5.1)	0
Dysphagia	3 (1.9)	0	19 (5.1)	2 (0.5)
Hyponatraemia	7 (4.4)	4 (2.5)	19 (5.1)	13 (3.5)
Hypotension	11 (6.9)	2 (1.3)	19 (5.1)	3 (0.8)
Myalgia	8 (5.0)	1 (0.6)	19 (5.1)	1 (0.3)
Platelet count decreased	8 (5.0)	1 (0.6)	18 (4.8)	4 (1.1)
Productive cough	9 (5.6)	0	18 (4.8)	0
Anxiety	8 (5.0)	1 (0.6)	16 (4.3)	1 (0.3)
Paraesthesia	9 (5.6)	0	15 (4.0)	0
Urinary tract infection	11 (6.9)	2 (1.3)	15 (4.0)	3 (0.8)
Hypoacusis	10 (6.3)	3 (1.9)	14 (3.8)	3 (0.8)
Pneumonitis	9 (5.6)	4 (2.5)	14 (3.8)	5 (1.3)
Stomatitis	8 (5.0)	0	13 (3.5)	0
Depression	8 (5.0)	0	12 (3.2)	0
Muscular weakness	8 (5.0)	2 (1.3)	12 (3.2)	4 (1.1)
Fall	8 (5.0)	0	11 (2.9)	0

AEs were graded according to the CTCAE V4.03. MedDRA version 24.0 was used.

Amongst MET-mutated patients, AEs suspected to be study drug related were reported in 90.6% of subjects. The most frequent AEs suspected to be study drug related (in ⩾ 20% of all subjects) were oedema peripheral (57.5%), nausea (37.5%) and blood creatinine increased (23.8%). In all A2201 subjects, AEs suspected to be study drug related were reported in 86.9% of subjects. The most frequent AEs suspected to be study drug related (in ⩾ 20% of all subjects) were oedema peripheral (172 subjects, 46.1%), nausea (130 subjects, 34.9%) and blood creatinine increased (77 subjects, 20.6%). However, the causality assessment is challenging due to the lack of control group and the open label nature of the study design.

2.6.6.3. Serious adverse event/deaths/other significant events

Serious adverse events

The findings (≥ 2% difference infrequency) were consistent between MET mutant subjects and all A2201 subjects except all-grades pneumonia (3.8% in MET mutant subjects vs. 5.9% in all A2201 subjects).

Table 58. Serious adverse events irrespective of study drug relationship by preferred term with an incidence ≥1% (all grades) in Study A2201 (Safety set) – DCO 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)
- Total	79 (49.4)	65 (40.6)	198 (53.1)	162 (43.4)
Dyspnoea	9 (5.6)	6 (3.8)	25 (6.7)	18 (4.8)
Pneumonia	6 (3.8)	6 (3.8)	22 (5.9)	17 (4.6)
Pleural effusion	5 (3.1)	1 (0.6)	16 (4.3)	8 (2.1)
General physical health deterioration	2 (1.3)	2 (1.3)	11 (2.9)	10 (2.7)
Vomiting	2 (1.3)	1 (0.6)	9 (2.4)	6 (1.6)
Nausea	1 (0.6)	1 (0.6)	7 (1.9)	6 (1.6)
Pulmonary embolism	1 (0.6)	1 (0.6)	7 (1.9)	7 (1.9)
Abdominal pain	1 (0.6)	1 (0.6)	6 (1.6)	5 (1.3)
Cellulitis	5 (3.1)	4 (2.5)	6 (1.6)	4 (1.1)
Hyponatraemia	2 (1.3)	2 (1.3)	6 (1.6)	5 (1.3)
Pneumonitis	5 (3.1)	4 (2.5)	6 (1.6)	5 (1.3)
Oedema peripheral	2 (1.3)	2 (1.3)	5 (1.3)	4 (1.1)
Pyrexia	2 (1.3)	2 (1.3)	5 (1.3)	2 (0.5)
Respiratory failure	2 (1.3)	2 (1.3)	5 (1.3)	5 (1.3)
Respiratory tract infection	0	0	5 (1.3)	5 (1.3)
Arthralgia	2 (1.3)	1 (0.6)	4 (1.1)	2 (0.5)
Cardiac failure	1 (0.6)	1 (0.6)	4 (1.1)	4 (1.1)
Non-cardiac chest pain	1 (0.6)	1 (0.6)	4 (1.1)	4 (1.1)
Peripheral swelling	2 (1.3)	1 (0.6)	4 (1.1)	1 (0.3)
Pneumothorax	1 (0.6)	0	4 (1.1)	1 (0.3)
Dehydration	3 (1.9)	3 (1.9)	3 (0.8)	3 (0.8)
Muscular weakness	2 (1.3)	2 (1.3)	3 (0.8)	3 (0.8)
Drug-induced liver injury	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Erysipelas	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Hypoacusis	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.3)
Interstitial lung disease	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Pyelonephritis	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Thrombocytopenia	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)

AEs were graded according to the CTCAE V4.03. MedDRA version 24.0 was used.

Deaths

Of the 14 on-treatment deaths due to "other" reasons, 12 were attributed to SAEs with a fatal outcome. (Table 59)

Table 59. On treatment deaths (Safety set) – Study A2201- DCO 30-Aug-2021

Primary system organ class Principal cause of death	All MET mutant subjects N=160 n(%)	All A2201 subjec N=373 n(%)
Total on-treatment death	28 (17.5)	62 (16.6)
Study Indication	20 (12.5)	48 (12.9)
Other Causes	8 (5.0)	14 (3.8)
Cardiac disorders		
-Total	2 (1.3)	4 (1.1)
Cardiac Arrest	0	2 (0.5)
Atrial Fibrillation	1 (0.6)	1 (0.3)
Cardiopulmonary Failure	1 (0.6)	1 (0.3)
General disorders and administration site conditions		
-Total	1 (0.6)	1 (0.3)
Sudden Death	1 (0.6)	1 (0.3)
Hepatobiliary disorders		
-Total	0	1 (0.3)
Hepatitis	0	1 (0.3)
Infections and infestations		
-Total	1 (0.6)	4 (1.1)
Pneumonia	0	1 (0.3)
Pneumonia Bacterial	0	1 (0.3)
Sepsis	0	1 (0.3)
Septic Shock	1 (0.6)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
-Total	20 (12.5)	48 (12.9)
Non-Small Cell Lung Cancer	20 (12.5)	48 (12.9)
Psychiatric disorders		
-Total	1 (0.6)	1 (0.3)
Assisted Suicide	1 (0.6)	1 (0.3)
Respiratory, thoracic and mediastinal disorders		
-Total	3 (1.9)	3 (0.8)
Organising Pneumonia	1 (0.6)	1 (0.3)
Pneumonitis	1 (0.6)	1 (0.3)
Respiratory Distress	1 (0.6)	1 (0.3)
SAEs with fatal outcome	6 (3.8)	12 (3.2)
Cardiac Arrest	0	2 (0.5)
Aspiration	1 (0.6)	1 (0.3)
Atrial Fibrillation	1 (0.6)	1 (0.3)
Cardiac Failure	1 (0.6)	1 (0.3)
Cardiopulmonary Failure	1 (0.6)	1 (0.3)
Hepatitis	0	1 (0.3)
Organising Pneumonia	1 (0.6)	1 (0.3)
Pneumonia	0	1 (0.3)
Pneumonia Bacterial	0	1 (0.3)
Pneumonitis	1 (0.6)	1 (0.3)
Respiratory Distress	1 (0.6)	1 (0.3)
Respiratory Failure	1 (0.6)	1 (0.3)
Sepsis	0	1 (0.3)
Septic Shock	1 (0.6)	1 (0.3)
Treatment related SAEs with fatal outcome	2 (1.3)	4 (1.1)
Cardiac Arrest	0	1 (0.3)
Hepatitis	0	1 (0.3)
Organising Pneumonia	1 (0.6)	1 (0.3)
Pneumonitis	1 (0.6)	1 (0.3)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported under "All A2201 subjects".
Deaths up to 30 days after the last dose are all included. MedDRA version 24.0 is used.

Adverse events of special interest (AESI)

AESIs were selected based on AEs that could be influenced by class of study drug, the mechanism of action and the current pre-clinical and clinical knowledge of the study drug: ILD/pneumonitis,

Hepatotoxicity, Renal dysfunction, CNS toxicity, Pancreatitis, Photosensitivity, Teratogenicity, DDI with strong CYP3A4 inducers, and QTc interval prolongation.

The findings were consistent between the MET mutant subjects and all A2201 subjects except for (≥ 5% difference in frequency) all grades renal dysfunction (35.0% in MET mutant subjects vs 28.4% in All A2201 subjects).

Table 60. Overview of adverse events of special interest (Safety set) – Study A2201 – DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
AESI	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Hepatotoxicity	55 (34.4)	19 (11.9)	119 (31.9)	41 (11.0)
Renal dysfunction	56 (35.0)	1 (0.6)	106 (28.4)	2 (0.5)
Central nervous system (CNS) toxicity	29 (18.1)	0	70 (18.8)	3 (0.8)
Pancreatitis	27 (16.9)	18 (11.3)	53 (14.2)	33 (8.8)
Interstitial lung disease and Pneumonitis[1]	12 (7.5)	7 (4.4)	20 (5.4)	8 (2.1)
QTc interval prolongation	3 (1.9)	0	10 (2.7)	3 (0.8)
Photosensitivity	1 (0.6)	0	1 (0.3)	0
Teratogenicity[2]	1 (0.6)	0	1 (0.3)	0
Drug-drug interactions with strong CYP3A4 inducers	0	0	0	0

Adverse events of interest are sorted in descending frequency of "All Grades" column, as reported under "All A2201 subjects".

Numbers (n) represent counts of subjects.

A subject with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 12-Oct-2021.

[1] ILD AESI was re-run for the SCS Update for the inclusion of the PT of 'organising pneumonitis' in the updated AESI grouping.

[2] Gilbert's syndrome was reported as AE for one subject (A2201-2005-029, 79-year-old female) and coded per MedDRA default hierarchy to primary SOC of "Congenital, familial and genetic disorders". However, there was no pregnancy reported in this study."

Interstitial lung disease/pneumonitis

The aggregated PTs used to identify this AESI are based on SMQ - Interstitial lung disease, and PTs using MedDRA version 24.0. ILD AESI was re-run for the SCS Update (with DCO of 30 Aug 2021) for the inclusion of the PT of 'organising pneumonitis' in the updated AESI grouping.

TKIs are known to be associated with an increased risk of ILD/pneumonitis.

Table 61. Incidence of adverse events of special interest – ILD/pneumonitis (Safety set) – Study A2201

	All MET mutant subjects N=160 n (%)	All A2201 subjects N=373 n (%)
Number of subjects with at least one event (95% CI)	12 (7.5) (3.9, 12.7)	20 (5.4) (3.3, 8.2)
Exposure-adjusted overall incidence, n (IR per 100 STM)	12 (0.6)	20 (0.7)
Maximum grade		
Grade 3 AEs	7 (4.4)	8 (2.1)
Grade 4 AEs	0	0
Grade 3/4 AEs	7 (4.4)	8 (2.1)
Suspected AEs	7 (4.4)	12 (3.2)
SAEs	8 (5.0)	10 (2.7)
Action taken		
Permanently discontinued	6 (3.8)	11 (2.9)
Dose adjusted	1 (0.6)	1 (0.3)
Temporarily interrupted	2 (1.3)	3 (0.8)
Not applicable	3 (1.9)	3 (0.8)
None	7 (4.4)	11 (2.9)
Medication or therapy taken	12 (7.5)	18 (4.8)
AE outcome		
Recovered/resolved	7 (4.4)	10 (2.7)
Recovering/resolving	4 (2.5)	7 (1.9)
Not recovered/not resolved	4 (2.5)	7 (1.9)
Recovered/resolved with sequelae	0	0
Fatal	2 (1.3)	2 (0.5)
Unknown	0	0

Interstitial lung disease/pneumonitis based on SMQ-Interstitial lung disease and Preferred Term organizing pneumonia.
MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 12-Oct-2021.

There was one fatal event of treatment related pneumonitis (0.6%) and one fatal event of organising pneumonia (0.6%). ILD/pneumonitis occurred in 6 of 63 patients (9.5%) with a history of prior radiotherapy and 6 of 97 patients (6.2%) who did not receive prior radiotherapy. Six patients (3.8%) discontinued Tabrecta due to ILD/pneumonitis among the MET mutant subjects. ILD/pneumonitis mostly occurred within approximately the first 3 months of treatment. The median time to onset of grade 3 or higher ILD/pneumonitis was 7.0 weeks (range: 0.7 to 88.4 weeks). The median duration of first occurrence of grade 3/4 interstitial lung disease/pneumonitis events was 2.6 weeks.

Hepatotoxicity

The aggregated PTs used to identify this AESI were based on Novartis MedDRA Query (NMQ-Hepatotoxicity (excl. neoplasms) [STANDARD] which includes the following MedDRA SMQs: cholestasis and jaundice of hepatic origin (SMQ), liver related investigations, signs and symptoms (SMQ), liver-related coagulation and bleeding disturbances (SMQ), hepatic failure, fibrosis and cirrhosis and other liver damage related conditions (SMQ) and hepatitis, noninfectious (SMQ) and PTs using MedDRA version 24.0.

Table 62. Incidence of adverse events of special interest – Hepatotoxicity (Safety set) – DCO 30-Aug-2021

	All MET mutant subjects N=160 n (%)	All A2201 subjects N=373 n (%)
Number of subjects with at least one event (95% CI)	55 (34.4) (27.1, 42.3)	119 (31.9) (27.2, 36.9)
Exposure-adjusted overall incidence, n (IR per 100 STM)	55 (4.2)	119 (5.2)
Maximum grade		
Grade 3 AEs	16 (10.0)	34 (9.1)
Grade 4 AEs	3 (1.9)	7 (1.9)
Grade 3/4 AEs	19 (11.9)	41 (11.0)
Suspected AEs	36 (22.5)	71 (19.0)
SAEs	3 (1.9)	6 (1.6)
Action taken		
Permanently discontinued	4 (2.5)	7 (1.9)
Dose adjusted	10 (6.3)	15 (4.0)
Temporarily interrupted	16 (10.0)	29 (7.8)
Not applicable	4 (2.5)	24 (6.4)
None	48 (30.0)	93 (24.9)
Medication or therapy taken	15 (9.4)	28 (7.5)
AE outcome		
Recovered/resolved	42 (26.3)	81 (21.7)
Recovering/resolving	29 (18.1)	57 (15.3)
Not recovered/not resolved	29 (18.1)	73 (19.6)
Recovered/resolved with sequelae	1 (0.6)	2 (0.5)
Fatal	0	1 (0.3)
Unknown	0	1 (0.3)

MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 12-Oct-2021.

The median time to first occurrence of grade 3/4 hepatotoxicity events (using descriptive statistics) (n=41) was 1.41 months and the median duration of first occurrence of grade 3/4 hepatotoxicity events was 0.49 months.

Any grade ALT/AST elevations were reported in 24 of 160 patients (15.0%). Grade 3 or 4 ALT/AST elevations were observed in 13 of 160 patients (8.1%) treated with Tabrecta. Two patients (1.3%) discontinued Tabrecta due to ALT/AST elevations. ALT/AST elevations mostly occurred within approximately the first 3 months of treatment. The median time-to-onset of grade 3 or higher ALT/AST elevations was 6.4 weeks (range: 2.1 to 17.9 weeks).

Renal dysfunction

The aggregated PTs used to identify this AESI was based on standardized MedDRA Query (SMQ- Acute renal failure), and PTs using MedDRA version 24.0.
In vitro, capmatinib has shown potent inhibition of the renal transporters MATE1 and MATE2k. It has been reported that 10% - 40% of serum creatinine could be cleared via active tubular secretion by these renal transporters in addition to renal glomerular filtration (Lepist et al 2014). Results from the DDI Study A2102 with healthy subjects, indirectly suggest that transient increase of serum creatinine levels may result from reversible inhibition of active renal transporters, in this case, likely MATE1 and MATE2k.

Table 63. Incidence of adverse events of special interest – Renal dysfunction (Safety set) – Study A2201 – DCO: 30-Aug-2021

	All MET mutant subjects N=160 n (%)	All A2201 subjects N=373 n (%)
Number of subjects with at least one event (95% CI)	56 (35.0) (27.6, 42.9)	106 (28.4) (23.9, 33.3)
Exposure-adjusted overall incidence, n (IR per 100 STM)	56 (4.4)	106 (5.2)
Maximum grade		
Grade 3 AEs	1 (0.6)	2 (0.5)
Grade 4 AEs	0	0
Grade 3/4 AEs	1 (0.6)	2 (0.5)
Suspected AEs	39 (24.4)	80 (21.4)
SAEs	0	3 (0.8)
Action taken		
Permanently discontinued	2 (1.3)	3 (0.8)
Dose adjusted	6 (3.8)	9 (2.4)
Temporarily interrupted	18 (11.3)	35 (9.4)
Not applicable	1 (0.6)	5 (1.3)
None	49 (30.6)	94 (25.2)
Medication or therapy taken	1 (0.6)	11 (2.9)
AE outcome		
Recovered/resolved	46 (28.8)	89 (23.9)
Recovering/resolving	10 (6.3)	22 (5.9)
Not recovered/not resolved	26 (16.3)	46 (12.3)
Recovered/resolved with sequelae	0	0
Fatal	0	0
Unknown	0	0

MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 12-Oct-2021.

CNS toxicity

The aggregated PTs used to identify this AESI was based on standardized MedDRA Queries (SMQs-convulsions, vestibular disorders, Parkinson-like events), and PTs using MedDRA version 24.0.

Table 64. Incidence of adverse events of special interest – CNS toxicity (Safety set) – Study A2201 – DCO 30-Aug-2021

	All MET mutant subjects N=160 n (%)	All A2201 subjects N=373 n (%)
Number of subjects with at least one event (95% CI)	29 (18.1) (12.5, 25.0)	70 (18.8) (14.9, 23.1)
Exposure-adjusted overall incidence, n (IR per 100 STM)	29 (1.9)	70 (2.7)
Maximum grade		
Grade 3 AEs	0	3 (0.8)
Grade 4 AEs	0	0
Grade 3/4 AEs	0	3 (0.8)
Suspected AEs	7 (4.4)	18 (4.8)
SAEs	0	6 (1.6)
Action taken		
Permanently discontinued	0	0
Dose adjusted	0	1 (0.3)
Temporarily interrupted	0	6 (1.6)
Not applicable	0	1 (0.3)
None	29 (18.1)	67 (18.0)
Medication or therapy taken	3 (1.9)	15 (4.0)
AE outcome		
Recovered/resolved	21 (13.1)	44 (11.8)
Recovering/resolving	3 (1.9)	6 (1.6)
Not recovered/not resolved	11 (6.9)	33 (8.8)
Recovered/resolved with sequelae	0	0
Fatal	0	0
Unknown	0	0

MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 12-Oct-2021.

The median time to first occurrence of grade 3/4 CNS toxicity events (using descriptive statistics) and the median duration of first occurrence grade 3/4 CNS toxicity events were 1.77 months and 0.62 months, respectively (same as reported in the original submission with DCO of 18 Sep 2021).
The preclinical changes observed in the thalamic region can cause a broad number of neurological and or psychiatric adverse events if they would also occur in humans, effect that are not limited to seizures and motor events, as included in the current definition used for CNS toxicity. Using the updated DCO of 30-Aug-2021, an additional review was performed assessing AEs concerning psychiatric disorders, sensory abnormalities, and decreases in alertness/consciousness. Most AEs occurred in low frequencies and only insomnia (9.1%), anxiety (4.3%), paraesthesia (4.0%), depression (3.2%), dysphonia (2.9%), confusional state (1.6%), hypoaesthesia (1.6%), dysgeusia (1.3%), sleep disorder (1.3%), somnolence (1.3%), taste disorder (1.3%), and depressed mood (1.1%) occurred in more than 1% of the A2201 population. In total 31.6% experienced an AE of CNS (thalamus) toxicity, and 2.4% had Grade 3, none had Grade 4. SAEs were reported in 2.4%, and also AEs leading to hospitalisation occurred in 2.4%. None led to discontinuation.

Pancreatitis

The aggregated PTs used to identify this AESI was based on Novartis MedDRA Query (NMQ-Acute pancreatitis (excluding non-specific symptoms) [STANDARD]) which includes all narrow terms of the acute pancreatitis SMQ, and PTs using MedDRA version 24.0.

Table 65. Incidence of adverse events of special interest – Pancreatitis (Safety set) – Study A2201 – DCO: 30-Aug-2021

	All MET mutant subjects N=160 n (%)	All A2201 subjects N=373 n (%)
Number of subjects with at least one event (95% CI)	27 (16.9) (11.4, 23.6)	53 (14.2) (10.8, 18.2)
Exposure-adjusted overall incidence, n (IR per 100 STM)	27 (1.7)	53 (2.0)
Maximum grade		
Grade 3 AEs	12 (7.5)	26 (7.0)
Grade 4 AEs	6 (3.8)	7 (1.9)
Grade 3/4 AEs	18 (11.3)	33 (8.8)
Suspected AEs	25 (15.6)	49 (13.1)
SAEs	1 (0.6)	2 (0.5)
Action taken		
Permanently discontinued	3 (1.9)	4 (1.1)
Dose adjusted	4 (2.5)	4 (1.1)
Temporarily interrupted	17 (10.6)	28 (7.5)
Not applicable	2 (1.3)	5 (1.3)
None	20 (12.5)	39 (10.5)
Medication or therapy taken	1 (0.6)	2 (0.5)
AE outcome		
Recovered/resolved	23 (14.4)	45 (12.1)
Recovering/resolving	10 (6.3)	17 (4.6)
Not recovered/not resolved	13 (8.1)	24 (6.4)
Recovered/resolved with sequelae	0	0
Fatal	0	0
Unknown	0	0

MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 12-Oct-2021.

The median time to first occurrence (using descriptive statistics) and the median duration of first occurrence grade 3/4 pancreatitis grouped events (n=33) were 1.81 months and 0.26 months, respectively (1.77 months and 0.26 months, respectively, at the original submission). The median time to onset of grade 3 or higher amylase/lipase elevations was 10.1 weeks (range: 2.3 to 68.0 weeks).

Photosensitivity

The aggregated PTs used to identify this AESI were based on the NMQ-Photosensitivity reactions and PTs using MedDRA version 24.0.

Only 1 (0.3%) subject (same as the original submission) reported grade 1 photosensitivity-grouped AESI (a non-serious treatment-related Photosensitivity reaction). This subject was MET mutant and had psoriasis at baseline, which was a confounding factor. The study recommended use of precautionary measures against sunlight and UV exposure (e.g., the use of sunscreen, protective clothing, and to avoid sunbathing or using a solarium)

Teratogenicity

The aggregated PTs used to identify this AESI were based on the Novartis MedDRA Query (NMQ-Pregnancy [PSUR] [STANDARD]). This NMQ includes the MedDRA SMQ-pregnancy and neonatal topics and the PTs: ectopic pregnancy under hormonal contraception, exposure via body fluid, failed forceps delivery, forceps delivery, and vacuum extractor delivery, using MedDRA version 24.0

One (0.3%) subject reported a teratogenicity-grouped AESI (non-serious, non-treatment-related), event PT was Gilbert's syndrome, reported in a 79-year-old female and was coded per MedDRA default hierarchy to primary SOC of "Congenital, familial and genetic disorders", and accordingly classified as a teratogenicity-grouped AESI. However, there was no pregnancy reported in this study.

DDI with strong CYP3A inducers

The aggregated PTs used to identify this AESI were based on the SMQ - Lack of efficacy/effect (in subjects with concomitant medications of strong CYP3A inducers) and PTs using MedDRA version 24.0.

Per Study A2201 protocol, any subject receiving treatment with strong inducers of CYP3A where these could not be discontinued ≥ 1 week prior to the start of treatment with capmatinib and for the duration of the study was to be excluded from the study. One subject received concomitant medication with phenytoin during the course of study. No events of DDI with strong CYP3A inducers were observed in any clinical study with capmatinib including Study A2201.

QTc interval prolongation

The aggregated PTs used to identify this AESI were based on the SMQ - Torsade de pointes/QT prolongation and PTs using MedDRA version 24.0.

Table 66. Incidence of adverse events of special interest – QTc interval prolongation (Safety set) – Study A2201

	All MET mutant subjects N=160 n (%)	All A2201 subjects N=373 n (%)
Number of subjects with at least one event (95% CI)	3 (1.9) (0.4, 5.4)	10 (2.7) (1.3, 4.9)
Exposure-adjusted overall incidence, n (IR per 100 STM)	3 (0.2)	10 (0.3)
Maximum grade		
Grade 3 AEs	0	1 (0.3)
Grade 4 AEs	0	2 (0.5)
Grade 3/4 AEs	0	3 (0.8)
Suspected AEs	0	3 (0.8)
SAEs	0	2 (0.5)
Action taken		
Permanently discontinued	0	0
Dose adjusted	0	0
Temporarily interrupted	0	0
Not applicable	0	1 (0.3)
None	3 (1.9)	9 (2.4)
Medication or therapy taken	0	0
AE outcome		
Recovered/resolved	3 (1.9)	7 (1.9)
Recovering/resolving	0	0
Not recovered/not resolved	0	1 (0.3)
Recovered/resolved with sequelae	0	0
Fatal	0	2 (0.5)
Unknown	0	0

Data cut-off for INC280A2201: 30-Aug-2021

MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 12-Oct-2021.

Other AESI-related aspects

Swallowing difficulties were not pre-defined as an AESI. However, due to the large size of the tablets, a concern was raised during the procedure related to their potential to cause swallowing difficulties.

As of the DCO of 30-Aug-2021, 19 (5.1%) subjects experienced dysphagia (all grades) regardless of causality in A2201 study. Three (1.9%) subjects experienced dysphagia in the MET mutated group (of which 1 was an SAE). The AEs of dysphagia were considered to be treatment related in two subjects and 5 subjects required dose adjustment/interruption. None of these AEs led to permanent treatment discontinuation.

Except for 1 subject, all other subjects with the AE of dysphagia had one or more contributingfactors such as metastatic cervical/paratracheal lymphadenopathy, oesophageal invasion of lung cancer, oesophagitis, laryngeal oedema, gastroesophageal reflux disease, laryngeal oedema, dysphonia, tumour pain, dyspepsia, haemoptysis, gastritis, gastroduodenitis, osteonecrosis of jaw, and oesophageal candidiasis.

Overall, 3 subjects experienced SAEs of dysphagia in A2201 study.

Safety data in MET mutant population

Additional data was provided to characterise the safety in the MET mutant population. A total of 107 subjects of the 160 MET mutated subjects (66.9%) reported to have at least one AESI with grade 3/4 events reported in 38 subjects (23.8%) (Table 67). In general, considering the indication and the demographics of the target population, treatment with capmatinib was tolerated well with 32.5% of AESIs leading to dose interruption and/or adjustment, 8.8% of subjects requiring permanent study treatment discontinuation, and 16.3% of subjects requiring additional therapy to manage these AESIs. In summary, the safety profile appears manageable with dose interruptions /adjustments /discontinuations and one patient died due to 'hepatotoxicity' AESI (PT – hepatitis). The crude incidence of oedema peripheral and blood creatinine increased appear to be higher in the MET mutated subjects as compared to the overall study population (Table 68.). However, this is owing to the better response to capmatinib leading to longer duration of exposure to capmatinib and is comparable to the overall study population in terms of exposure adjusted incidence rates.

Table 67. AESI regardless of study drug relationship – MET mutant subjects (Safety set) – DCO: 30-Aug-2021

	All Mutant subjects N=160						
AESI	**AE n (%)**	**Grade 3/4 AE n (%)**	**SAE n (%)**	**Medication or treatment taken [1] n (%)**	**Dose interruption / adjustment [2] n (%)**	**Permanent Discontinuation [3] n (%)**	**Death (other reason) [4] n (%)**
Number of subjects with at least one AESI event	107 (66.9)	38 (23.8)	10 (6.3)	26 (16.3)	52 (32.5)	14 (8.8)	1 (0.6)
Renal dysfunction	56 (35.0)	1 (0.6)	0	1 (0.6)	20 (12.5)	2 (1.3)	0
Hepatotoxicity	55 (34.4)	19 (11.9)	3 (1.9)	15 (9.4)	20 (12.5)	4 (2.5)	0
Central nervous system (CNS) toxicity	29 (18.1)	0	0	3 (1.9)	0	0	0
Pancreatitis	27 (16.9)	18 (11.3)	1 (0.6)	1 (0.6)	17 (10.6)	3 (1.9)	0
Interstitial lung disease and Pneumonitis	11 (6.9)	6 (3.8)	7 (4.4)	11 (6.9)	3 (1.9)	5 (3.1)	1 (0.6)
QTc interval prolongation	3 (1.9)	0	0	0	0	0	0
Photosensitivity	1 (0.6)	0	0	0	0	0	0
Teratogenicity	1 (0.6)	0	0	0	0	0	0

Numbers (n) represent counts of subjects.

MedDRA version 24.0, CTCAE version V4.03, Case Retrieval Strategy version 12OCT2021.

[1] AEs with other action taken = Concomitant medication or non-drug therapy

[2] AEs with with action taken to the study drug = Dose adjusted or temporarily interrupted

[3] AEs with with action taken to the study drug = Permanently discontinued

[4] AEs with outcome = Fatal

Table 68. Preferred term regardless of study drug relationship – MET mutant subjects (Safety set) -DCO: 30-Aug-2021

	All Mutant subjects N=160						
Preferred term	**AE n (%)**	**Grade 3/4 AE n (%)**	**SAE n (%)**	**Medication or treatment taken [1] n (%)**	**Dose interruption /adjustment [2] n (%)**	**Permanent Discontinuation [3] n (%)**	**Death (other reason) [4] n (%)**
Number of subjects with at least one event	158 (98.8)	117 (73.1)	79 (49.4)	145 (90.6)	105 (65.6)	31 (19.4)	6 (3.8)
Oedema peripheral	104 (65.0)	22 (13.8)	2 (1.3)	66 (41.3)	37 (23.1)	4 (2.5)	0
Nausea	71 (44.4)	1 (0.6)	1 (0.6)	44 (27.5)	15 (9.4)	0	0
Blood creatinine increased	54 (33.8)	1 (0.6)	0	1 (0.6)	20 (12.5)	2 (1.3)	0
Fatigue	40 (25.0)	7 (4.4)	0	1 (0.6)	6 (3.8)	1 (0.6)	0
Vomiting	40 (25.0)	1 (0.6)	2 (1.3)	10 (6.3)	10 (6.3)	0	0
Dyspnoea	36 (22.5)	11 (6.9)	9 (5.6)	15 (9.4)	6 (3.8)	0	0
Decreased appetite	34 (21.3)	2 (1.3)	1 (0.6)	7 (4.4)	6 (3.8)	0	0

Numbers (n) represent counts of subjects.

Most frequently reported preferred terms are selected (more than 20% in all A2201 subjects).

MedDRA version 24.0, CTCAE version V4.03.

[1] AEs with other action taken = Concomitant medication or non-drug therapy

[2] AEs with action taken to the study drug = Dose adjusted or temporarily interrupted

[3] AEs with action taken to the study drug = Permanently discontinued

[4] AEs with outcome = Fatal

Safety data from non-overlapping data cohorts for NSCLC patients and All solid tumour subjects

Safety data was also compared for the A2201 study population (n=373), NSCLC patients that were treated in other studies than A2201 (n=85), and solid tumour patients excluding the patients that were treated in A2201 (n=207).

The proportion of patients experiencing a Grade 3-4 AE was lower in the solid tumour patients excluding A2201 (57.0%) compared to A2201 patients (70.2%) and NSCLC patients excluding A2201 (70.6%). Regarding the type of AEs, regardless of study drug relationship, oedema peripheral was most commonly observed in the A2201 pool (all grades - 54.4%, Grade 3-4 - 9.9%) with lower incidences in the NSCLC excluding A2201 (all grades - 43.5%, Grade 3-4 - 3.5%) and solid tumours excluding A2201 (all grades - 37.7%, Grade 3-4 - 1.4%). A similar trend was seen for blood creatinine increased. This was reported in 27.1% in the A2201 pool (Grade 3-4 - 0.3%), 20.0% in the NSCLC pool excluding A2201 (Grade 3-4 - 0%), and 16.9% in the solid tumour pool excluding A2201 (grade 3-4 - 0.5%). When looking at treatment-related AEs, a similar trend of higher incidences of oedema peripheral and blood creatinine increased in the A2201 population was observed.

SAEs were reported for 53.1% in the A2201 population, 49.4% of the NSCLC population excluding A2201, and 44.0% of the solid tumour pool excluding A2201. AEs leading to permanent discontinuation of the study drug were reported for 17.4% in the A2201 population, 17.6% of the NSCLC population excluding A2201, and 12.6% of the solid tumour pool excluding A2201. The type of SAEs and AEs leading to study drug discontinuations were similar between the pools.

The incidences of on-treatment deaths were consistent with 16.6% in the A2201 pool, 14.1% in the NCSLC pool excluding A2201, and 14.0% in the solid tumour pool excluding A2201. Other causes for deaths than the study indications were reported in 3.8%, 5.9%, and 7.2%, respectively.

Adverse drug reactions

MedDRA version 24.0 in line with DCO of 30-Aug-2021 and CTCAE version 4.03 were applied for the ADRs. Screening for candidates for ADR was performed by applying quantitative criteria (≥ 10% of all AEs and ≥ 3% of grade 3/4 events from Study A2201). In addition, screening for ADR candidates included all AEs leading to discontinuation, all AEs suspected by the investigator as treatment-related, preferred terms captured by search terms in CRS of the safety risk profile/management plan, all laboratory abnormalities, all SAEs, all deaths (except those due to disease progression), and the applicant's designated medical events.

Medical judgment for the final decision to include or rule out an association of an AE with capmatinib was taken based on Bradford Hill criteria, biologic plausibility, and HA commitments to report or follow-up.

The CMQ grouping for the ADR rash is based on MedDRA version 24.1 in line with the date of identification of this new ADR. This ADR term comprises a grouping of PTs, which includes Rash, Rash macular, Rash maculopapular, Rash erythematous, and Rash vesicular. This ADR of rash is mostly represented by grade 1/2 AEs without any SAEs or AEs leading to permanent discontinuation of study treatment.

Table 69: **Adverse reactions in patients (N=160) harbouring METex14 skipping alterations in study GEOMETRY mono-1 (Data cut-off: 30-Aug-2021)**

Adverse reaction	**All grades Frequency category**	**All grades %**	**Grade 3/4 %**
Infections and infestations			
Cellulitis	Common	4.4	2.5*
Metabolism and nutrition disorders			
Decreased appetite	Very common	21.3	1.3*
Respiratory, thoracic, and mediastinal disorders			
Dyspnoea	Very common	22.5	6.9*
Cough	Very common	17.5	0.6*
ILD/pneumonitis[1]	Common	6.9	4.4*
Gastrointestinal disorders			
Vomiting	Very common	25.0	0.6*
Nausea	Very common	44.4	0.6*
Diarrhoea	Very common	15.6	-
Constipation	Very common	13.1	1.3*
Skin and subcutaneous tissue disorders			
Pruritus	Very common	10.6	0.6*
Rash[2]	Common	-	-
Urticaria	Common	2.5	0.6*
General disorders and administration site conditions			
Oedema peripheral[3]	Very common	68	14.4*

Pyrexia	Very common	10.6	1.3*
Fatigue[4]	Very common	34.4	8.1*
Back pain	Very common	20.6	1.3*
Weight decreased	Very common	12.5	-
Non-cardiac chest pain[5]	Common	9.4	1.3*
Investigations			
Albumin decreased	Very common	78.3	1.9*
Creatinine increased	Very common	74.5	0.6*
Alanine aminotransferase increased	Very common	45.9	11.5
Amylase increased	Very common	37.2	7.1
Lipase increased	Very common	33.3	11.5
Aspartate aminotransferase increased	Very common	33.8	5.7
Phosphate decreased	Very common	30.1	4.5
Sodium decreased	Very common	22.3	4.5
Bilirubin increased	Common	8.3	0.6*

1 ILD/pneumonitis includes preferred terms (PTs) of ILD, pneumonitis and organising pneumonia.
2 Rash includes PTs of rash, rash maculopapular and rash vesicular.
3 Oedema peripheral includes PTs of oedema peripheral and peripheral swelling.
4 Fatigue includes PTs of fatigue and asthenia.
5 Non-cardiac chest pain includes PTs of chest discomfort, musculoskeletal chest pain and non-cardiac chest pain.
* No grade 4 adverse reactions reported in GEOMETRY mono-1 MET-mutated patients.
Cases of acute kidney injury (n=1), renal failure (n=4) and acute pancreatitis (n=1) were reported in GEOMETRY mono-1 MET-amplified patients.

2.6.6.4. Laboratory findings

Haematology

Study A2201: Haematological abnormalities were predominantly grade 1/2.

Table 70: Worst post-baseline haematology abnormalities based on CTC grades (safety set) – Study A2201 -DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hemoglobin (g/L), Blood - decrease	87 (54.4)	3 (1.9)	224 (60.1)	10 (2.7)
Leukocytes (10E9/L), Blood - decrease	62 (38.8)	2 (1.3)	100 (26.8)	6 (1.6)
Lymphocytes (10E9/L), Blood - decrease	110 (68.8)	30 (18.8)	222 (59.5)	60 (16.1)
Lymphocytes (10E9/L), Blood - increase	2 (1.3)	0	5 (1.3)	0
Neutrophils (10E9/L), Blood - decrease	38 (23.8)	4 (2.5)	65 (17.4)	11 (2.9)
Platelets (10E9/L), Blood - decrease	37 (23.1)	2 (1.3)	66 (17.7)	6 (1.6)

Data cut-off for INC280A2201: 30-Aug-2021
Grades based on CTCAE version V4.03.

Clinical chemistry

Clinical chemistry abnormalities were predominantly grade 1/2.

Table 71: Worst post-baseline clinical chemistry abnormalities based on CTC grades (safety set) – Study A2201 - DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Alanine Aminotransferase (U/L) - increase	75 (46.9)	18 (11.3)	151 (40.5)	34 (9.1)
Albumin (g/L) - decrease	135 (84.4)	3 (1.9)	283 (75.9)	7 (1.9)
Alkaline Phosphatase (U/L) - increase	88 (55.0)	3 (1.9)	175 (46.9)	3 (0.8)
Amylase (U/L) - increase	64 (40.0)	11 (6.9)	141 (37.8)	17 (4.6)
Aspartate Aminotransferase (U/L) - increase	61 (38.1)	9 (5.6)	113 (30.3)	21 (5.6)
Bilirubin (umol/L) - increase	13 (8.1)	1 (0.6)	30 (8.0)	4 (1.1)
Calcium Corrected (mmol/L) - decrease	6 (3.8)	0	6 (1.6)	0
Calcium Corrected (mmol/L) - increase	0	0	1 (0.3)	0
Creatinine (umol/L) - increase	128 (80.0)	1 (0.6)	259 (69.4)	2 (0.5)
Gamma Glutamyl Transferase (U/L) - increase	73 (45.6)	14 (8.8)	169 (45.3)	31 (8.3)
Glucose (mmol/L) - decrease	55 (34.4)	0	87 (23.3)	1 (0.3)
Lipase (U/L) - increase	55 (34.4)	18 (11.3)	109 (29.2)	33 (8.8)
Magnesium (mmol/L) - decrease	22 (13.8)	0	60 (16.1)	0
Magnesium (mmol/L) - increase	14 (8.8)	1 (0.6)	25 (6.7)	2 (0.5)
Phosphate (mmol/L) - decrease	54 (33.8)	7 (4.4)	104 (27.9)	16 (4.3)
Potassium (mmol/L) - decrease	18 (11.3)	3 (1.9)	37 (9.9)	8 (2.1)
Potassium (mmol/L) - increase	48 (30.0)	7 (4.4)	90 (24.1)	15 (4.0)
Sodium (mmol/L) - decrease	41 (25.6)	8 (5.0)	97 (26.0)	24 (6.4)
Sodium (mmol/L) - increase	9 (5.6)	0	22 (5.9)	0
Urate (umol/L) - increase	16 (10.0)	2 (1.3)	33 (8.8)	2 (0.5)

Data cut-off for INC280A2201: 30-Aug-2021
Grades based on CTCAE version V4.03.

Liver function tests

Most of the liver enzyme elevations were grade 1/2. One (0.3%) subject had ALT/AST > 3 × ULN & BILI> 2 × ULN & ALP < 2 × ULN (Table 72). None of the abnormalities met the criteria of confirmed DILI/Hy's law cases. Upon medical review, this case did not meet the criteria of confirmed DILI/Hy's law cases.

Table 72: Categorical analysis of hepatic laboratory values (Safety set) – Study A2201 - DCO: 30-Aug-2021

	All MET mutant subjects N=160 n (%)	All A2201 subjects N=373 n (%)
Peak post-baseline values		
ALT > 3xULN	26 (16.3)	50 (13.4)

ALT > 5xULN	18 (11.3)	34 (9.1)
ALT > 8xULN	11 (6.9)	20 (5.4)
ALT > 10xULN	7 (4.4)	15 (4.0)
ALT > 20xULN	3 (1.9)	6 (1.6)
AST > 3xULN	19 (11.9)	37 (9.9)
AST > 5xULN	9 (5.6)	21 (5.6)
AST > 8xULN	4 (2.5)	8 (2.1)
AST > 10xULN	3 (1.9)	6 (1.6)
AST > 20xULN	2 (1.3)	4 (1.1)
ALT and/or AST > 3xULN	27 (16.9)	52 (13.9)
ALT and/or AST > 5xULN	18 (11.3)	34 (9.1)
ALT and/or AST > 8xULN	11 (6.9)	20 (5.4)
ALT and/or AST > 10xULN	7 (4.4)	15 (4.0)
ALT and/or AST > 20xULN	3 (1.9)	6 (1.6)
Total Bilirubin > 2xULN	3 (1.9)	6 (1.6)
Total Bilirubin > 3xULN	1 (0.6)	4 (1.1)
Combined and concurrent values post-baseline		
ALT or AST > 3xULN & BILI> 2xULN	2 (1.3)	3 (0.8)
ALT or AST > 3xULN & BILI> 2xULN & ALP ≥ 2xULN	1 (0.6)	2 (0.5)
ALT or AST > 3xULN & BILI> 2xULN & ALP < 2xULN	1 (0.6)	1 (0.3)
Combined elevations values post-baseline		
ALT or AST > 3xULN & BILI> 2xULN	2 (1.3)	4 (1.1)
ALT or AST > 3xULN & BILI> 2xULN & ALP ≥ 2xULN	1 (0.6)	3 (0.8)
ALT or AST > 3xULN & BILI> 2xULN & ALP < 2xULN	1 (0.6)	1 (0.3)
Combined elevations values post-baseline by baseline levels		
AST and ALT <= ULN at baseline		
ALT or AST >3xULN & BILI >2xULN	2 (1.3)	4 (1.1)
ALT or AST >3xULN & BILI >2xULN & ALP ≥ 2xULN	1 (0.6)	3 (0.8)
ALT or AST >3xULN & BILI >2xULN & ALP <2xULN	1 (0.6)	1 (0.3)
ALT or AST > ULN at baseline		
Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN)	0	0
Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP ≥ 2x ULN	0	0
Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP <2x ULN	0	0

Data cut-off for INC280A2201: 30-Aug-2021

ALT=alanine aminotransferase, ALP=alkaline phosphatase, AST= aspartate aminotransferase, ULN=Upper Limit of Normal range

Concurrent measurements are those occurring in the same assessment sample. Combined elevations based on the peak values at any post-baseline time for a subject.

* Elevated AST or ALT defined as: >3x ULN if ≤ ULN at baseline, or (>3x Bsl or 8x ULN) if > ULN at baseline

Baseline is defined as the last non-missing value prior to or on the first dosing date.

Vital signs

In the original submission, the most commonly reported (> 15% subjects) vital sign change abnormalities were weight increase ≥ 10%(19.8%) and pulse rate ≥ 100 bpm with increase ≥ 25% (15.8%). No unexpected clinically important abnormalities were reported between the DCO for the original submission (18-Sep-2020) and the cut-off for this Safety Update (30-Aug-2021).

Electrocardiograms

No subject had a QTcF interval >500 ms, and 3 subjects had QTcF value of >480 ms to ≤ 500 ms. None of the QTcF values > 480 ms was associated with cardiac clinical symptoms or arrhythmias. A total of 116 subjects took concomitant medications which have a risk of causing QTc prolongation, but none of them experienced a post-dose QTcF interval > 480 ms.

2.6.6.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.6.6. Safety in special populations

Age

Table 73. Number of subjects in each age subgroup in study A2201 - DCO: 30-Aug-2021

Table 6-1 Number of subjects in each age subgroup

	<65 years n (%)	≥65-<75 years n (%)	≥75-<85 years n (%)	>85 years n (%)
1L MET mutated (N=60)	6 (10.0)	29 (48.3)	22 (36.7)	3 (5.0)
All MET mutated (N=160)	24 (15.0)	82 (51.3)	47 (29.4)	7 (4.4)
All A2201 subjects (N=373)	147 (39.4)	157 (42.1)	60 (16.1)	9 (2.4)

The incidence of Blood creatinine increased and Oedema peripheral increased with age; the incidence of Nausea, Fatigue, Decreased appetite and Dyspnoea was similar (difference < 10% subjects) across subgroups; the incidence of Vomiting was similar for <65 years subgroup and ≥ 65 - 75 years subgroup, but lower in ≥ 75 – 85 years subgroup.

Table 74. Adverse events by preferred term with an incidence ≥20% (all grades) in Study A2201/ All NSCLC subjects/ All solid tumour subjects – Subgroup: Age (excluding ≥85 years) (Safety set) - (DCO 30 Aug 2021)

	Study A2201						All NSCLC subjects						All solid tumor subjects					
	< 65 N=147		≥ 65 - < 75 N=157		≥ 75 - < 85 N=60		< 65 N=196		≥ 65 - < 75 N=187		≥ 75 - < 85 N=65		< 65 N=280		≥ 65 - < 75 N=221		≥ 75 - < 85 N=69	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Number of subjects with at least one event	**145 (98.6)**	**96 (65.3)**	**153 (97.5)**	**111 (70.7)**	**60 (100)**	**45 (75.0)**	**194 (99.0)**	**130 (66.3)**	**183 (97.9)**	**134 (71.7)**	**65 (100)**	**47 (72.3)**	**277 (98.9)**	**175 (62.5)**	**217 (98.2)**	**145 (65.6)**	**69 (100)**	**49 (71.0)**
Oedema peripheral	67 (45.6)	8 (5.4)	88 (56.1)	15 (9.6)	40 (66.7)	12 (20.0)	83 (42.3)	8 (4.1)	105 (56.1)	17 (9.1)	43 (66.2)	13 (20.0)	110 (39.3)	8 (2.9)	118 (53.4)	17 (7.7)	44 (63.8)	13 (18.8)
Nausea	61 (41.5)	3 (2.0)	76 (48.4)	5 (3.2)	25 (41.7)	1 (1.7)	89 (45.4)	4 (2.0)	87 (46.5)	7 (3.7)	29 (44.6)	1 (1.5)	125 (44.6)	7 (2.5)	103 (46.6)	7 (3.2)	32 (46.4)	1 (1.4)
Vomiting	45 (30.6)	4 (2.7)	50 (31.8)	4 (2.5)	10 (16.7)	1 (1.7)	67 (34.2)	5 (2.6)	56 (29.9)	6 (3.2)	12 (18.5)	1 (1.5)	95 (33.9)	9 (3.2)	67 (30.3)	6 (2.7)	13 (18.8)	1 (1.4)
Blood creatinine increased	26 (17.7)	0	46 (29.3)	0	24 (40.0)	0	34 (17.3)	0	55 (29.4)	0	24 (36.9)	0	44 (15.7)	1 (0.4)	63 (28.5)	0	24 (34.8)	0
Fatigue	27 (18.4)	5 (3.4)	43 (27.4)	10 (6.4)	11 (18.3)	1 (1.7)	42 (21.4)	7 (3.6)	50 (26.7)	10 (5.3)	12 (18.5)	1 (1.5)	68 (24.3)	12 (4.3)	55 (24.9)	10 (4.5)	13 (18.8)	1 (1.4)
Dyspnoea	32 (21.8)	12 (8.2)	42 (26.8)	9 (5.7)	11 (18.3)	3 (5.0)	51 (26.0)	15 (7.7)	48 (25.7)	11 (5.9)	11 (16.9)	3 (4.6)	60 (21.4)	16 (5.7)	52 (23.5)	11 (5.0)	12 (17.4)	3 (4.3)
Decreased appetite	27 (18.4)	2 (1.4)	36 (22.9)	1 (0.6)	13 (21.7)	1 (1.7)	36 (18.4)	3 (1.5)	47 (25.1)	1 (0.5)	15 (23.1)	2 (3.1)	57 (20.4)	4 (1.4)	55 (24.9)	1 (0.5)	17 (24.6)	2 (2.9)
Constipation	25 (17.0)	2 (1.4)	34 (21.7)	0	9 (15.0)	0	33 (16.8)	2 (1.0)	39 (20.9)	1 (0.5)	9 (13.8)	0	48 (17.1)	4 (1.4)	44 (19.9)	1 (0.5)	9 (13.0)	0
Cough	21 (14.3)	1 (0.7)	27 (17.2)	1 (0.6)	12 (20.0)	0	30 (15.3)	1 (0.5)	32 (17.1)	1 (0.5)	12 (18.5)	0	35 (12.5)	1 (0.4)	35 (15.8)	1 (0.5)	12 (17.4)	0
Diarrhoea	30 (20.4)	1 (0.7)	26 (16.6)	1 (0.6)	9 (15.0)	0	38 (19.4)	2 (1.0)	35 (18.7)	2 (1.1)	11 (16.9)	0	55 (19.6)	3 (1.1)	43 (19.5)	2 (0.9)	13 (18.8)	0

Numbers (n) represent counts of subjects. A subject with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 24.0, CTCAE version 4.03.

Regarding the overall adverse event profile per age group, high level assessment shows that the elderly patients present a higher frequency of AEs leading to discontinuation and treatment interruption. However, the number of patients is small and therefore not conclusive.

Table 75 - Adverse event profile per age group in study A2201 (DCO 30 Aug 2021)

	All subjects N=373							
Age group (years)	**< 65**		**65-<75**		**75-<85**		**≥85**	
Patient numbers	**n=147**		**n=157**		**n=60**		**n=9**	
	all grades	**grade 3/4**	**all grades**	**grade 3/4**	**all grades**	**grade 3/4**	**all grades**	**grade 3/4**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
all AE's	145 (98.6)	96 (65.3)	153 (97.5)	111 (70.7)	60 -100	45 (75.0)	9 (100)	4 (44.4)
AE treatment related	117 (79.6)	42 (28.6)	140 (89.2)	71 (45.2)	58 (96.7)	30 (50.0)	9 (100)	4 (44.4)
AE discontinuation	22 **(15.0)**	14 (9.5)	25 (15.9)	16 (10.2)	13 **(21.7)**	9 (15.0)	0	0
AE adjustment interruption	77 **(52.4)**	53 (36.1)	101 (64.3)	70 (44.6)	44 **(73.3)**	32 (53.3)	6 (66.7)	3 (33.3)
SAEs	79 **(53.7)**	70 (47.6)	82 (52.2)	61 (38.9)	25 **(41.7)**	22 (36.7)	4 (44.4)	3 (33.3)
SAEs treatment related	15 (10.2)	10 (6.8)	27 (17.2)	20 (12.7)	5 (8.3)	3 (5.0)	2 (22.2)	2 (22.2)

The following table reflects data from the elderly population included in study A2201 (overall population, not separating according to MET-status).

Table 76 Key safety results by age categories in study A2201 (Safety set) (DCO 30-Aug-2021)

	All subjects N=373			
MedDRA Terms	**Age <65 years N=147 n (%)**	**Age 65-< 75 years N=157 n (%)**	**Age 75-<85 years N=60 n (%)**	**Age ≥85 years N=9 n (%)**
Total AEs	**145 (98.6)**	**153 (97.5)**	**60 (100.0)**	**9 (100.0)**
Serious AEs – Total	81 (55.1)	83 (52.9)	28 (46.7)	6 (66.7)
- Fatal	3 (2.0)	6 (3.8)	3 (5.0)	0
- Hospitalization/prolong existing hospitalization	77 (52.4)	76 (48.4)	25 (41.7)	6 (66.7)
- Life-threatening	8 (5.4)	2 (1.3)	1 (1.7)	0
- Significant Disability	1 (0.7)	5 (3.2)	0	0
- Congenital anomaly or birth defect	0	0	0	0
- Other (medically significant)	6 (4.1)	9 (5.7)	3 (5.0)	0
AE leading to drop-out [1]	24 (16.3)	26 (16.6)	15 (25.0)	0
Psychiatric disorders [2]	31 (21.1)	37 (23.6)	11 (18.3)	2 (22.2)
Nervous system disorders [2]	43 (29.3)	48 (30.6)	20 (33.3)	5 (55.6)
Accidents and injuries [3]	9 (6.1)	21 (13.4)	9 (15.0)	2 (22.2)
Cardiac disorders [2]	22 (15.0)	16 (10.2)	12 (20.0)	1 (11.1)
Vascular disorders [2]	20 (13.6)	24 (15.3)	15 (25.0)	0
Cerebrovascular disorders [3]	7 (4.8)	7 (4.5)	0	2 (22.2)

	All subjects N=373			
MedDRA Terms	**Age <65 years N=147 n (%)**	**Age 65-< 75 years N=157 n (%)**	**Age 75-<85 years N=60 n (%)**	**Age ≥85 years N=9 n (%)**
Infections and infestations [2]	62 (42.2)	55 (35.0)	22 (36.7)	4 (44.4)
Anticholinergic syndrome [3]	55 (37.4)	50 (31.8)	17 (28.3)	2 (22.2)
Quality of life decreased [4]	NA	NA	NA	NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [5]	12 (8.2)	22 (14.0)	9 (15.0)	3 (33.3)

Numbers (n) represent counts of patients. MedDRA version 24.0, CTCAE version V4.03.
[1] AEs leading to drop-out are TEAEs leading to permanent discontinuation of study drug
[2] As per primary System Organ Class
[3] As per MedDRA SMQs (broad): Accidents and Injuries (SMQ: Accidents and Injuries), Cerebrovascular disorders (SMQ: Central nervous system vascular disorders), and Anticholinergic syndrome (SMQ: Anticholinergic syndrome).
[4] No analysis of QoL by age was done for Study CINC280A2201
[5] The "Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures" includes the PTs of Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, and the HLGT of Fractures

The most frequent AEs (per PT) in the elderly population in study A2201 are shown in the following table (DCO 30 August 2021). Data are not broken down by MET-status.

Table 77. Preferred terms appearing more frequently in elderly patients, by age category in study A2201 (Safety set) (DCO 30-Aug-2021)

	All subjects N=373			
MedDRA Preferred Terms*	**Age <65 years N=147 n (%)**	**Age 65-< 75 years N=157 n (%)**	**Age 75-<85 years N=60 n (%)**	**Age ≥85 years N=9 n (%)**
Total AEs	**145 (98.6)**	**153 (97.5)**	**60 (100.0)**	**9 (100.0)**
Blood creatinine increased	26 (17.7)	47 (29.9)	25 (41.7)	3 (33.3)
Oedema peripheral	67 (45.6)	89 (56.7)	40 (66.7)	7 (77.8)
Hypocalcaemia	1 (0.7)	14 (8.9)	7 (11.7)	0
Fatigue	27 (18.4)	46 (29.3)	11 (18.3)	2 (22.2)
Nausea	61 (41.5)	77 (49.0)	26 (43.3)	6 (66.7)
Alanine aminotransferase increased	16 (10.9)	26 (16.6)	10 (16.7)	1 (11.1)

Numbers (n) represent counts of patients.
MedDRA version 24.0, CTCAE version V4.03.
*Preferred terms appearing more frequently in elderly patients are selected (more than 5% difference between the subgroups < 65 years and ≥ 65 years).

In the original submission, the AESIs and the respective PTs with incidences ≥ 10% in age subgroups and also with a difference ≥ 5% across subgroups in the sequence of <65 years vs. ≥ 65 to < 75 years vs. ≥ 75 to < 85 years age subgroups, respectively: CNS toxicity-grouped AESI: 13.6%, 19.1% and 26.7%; Renal dysfunction-grouped AESI: 18.4%, 31.8%, 40.0%; Blood creatinine increased: 17.7%, 29.3% and 40.0%.

Gender (DCO 18-Sep-2020)

Table 78 summarizes AEs with incidences ≥ 20% in any gender.

Table 78. Adverse events by preferred term with an incidence ≥20% (all grades) in Study A2201/ All NSCLC subjects/ All solid tumour subjects – Subgroup: Gender (Safety set) (DCO 18-Sep-2020)

	Study A2201				All NSCLC subjects				All solid tumor subjects			
	Female N=164		Male N=209		Female N=200		Male N=258		Female N=242		Male N=338	
Preferred Term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Number of subjects with at least one event	**162 (98.8)**	**101 (61.6)**	**205 (98.1)**	**155 (74.2)**	**198 (99.0)**	**126 (63.0)**	**254 (98.4)**	**190 (73.6)**	**240 (99.2)**	**145 (59.9)**	**333 (98.5)**	**229 (67.8)**
Oedema peripheral	100 (61.0)	16 (9.8)	102 (48.8)	20 (9.6)	112 (56.0)	17 (8.5)	127 (49.2)	22 (8.5)	124 (51.2)	17 (7.0)	156 (46.2)	22 (6.5)
Nausea	84 (51.2)	4 (2.4)	84 (40.2)	5 (2.4)	106 (53.0)	7 (3.5)	105 (40.7)	5 (1.9)	129 (53.3)	9 (3.7)	137 (40.5)	6 (1.8)
Vomiting	51 (31.1)	5 (3.0)	54 (25.8)	4 (1.9)	69 (34.5)	7 (3.5)	66 (25.6)	5 (1.9)	87 (36.0)	8 (3.3)	88 (26.0)	8 (2.4)
Blood creatinine increased	47 (28.7)	0	52 (24.9)	0	51 (25.5)	0	65 (25.2)	0	58 (24.0)	0	76 (22.5)	1 (0.3)
Fatigue	34 (20.7)	10 (6.1)	49 (23.4)	6 (2.9)	46 (23.0)	12 (6.0)	60 (23.3)	6 (2.3)	53 (21.9)	12 (5.0)	85 (25.1)	11 (3.3)
Constipation	21 (12.8)	1 (0.6)	48 (23.0)	2 (1.0)	29 (14.5)	2 (1.0)	53 (20.5)	2 (0.8)	36 (14.9)	3 (1.2)	66 (19.5)	3 (0.9)
Dyspnoea	40 (24.4)	12 (7.3)	47 (22.5)	13 (6.2)	51 (25.5)	13 (6.5)	61 (23.6)	17 (6.6)	53 (21.9)	13 (5.4)	73 (21.6)	18 (5.3)
Decreased appetite	37 (22.6)	2 (1.2)	42 (20.1)	2 (1.0)	45 (22.5)	3 (1.5)	56 (21.7)	3 (1.2)	55 (22.7)	4 (1.7)	77 (22.8)	3 (0.9)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.1, CTCAE version 4.03.

The AESIs and the respective PTs with incidences ≥ 10% in both subgroups and also with a difference ≥ 5% between subgroups are presented in the sequence of female vs. male subgroups, respectively: Hepatotoxicity-grouped AESI: 25.6% vs. 34.4%.

Race (DCO 18-Sep-2020)

The predominant race was Caucasian followed by Asian and the number of subjects in the "others" category was limited. As no definitive conclusions could be reached regarding AEs in the "others" subgroup, it has not been included for comparison.

Table 79. Adverse events by preferred term with an incidence ≥20% (all grades) in Study A2201/ All NSCLC subjects/ All solid tumor subjects – Subgroup: Race (Safety set) (DCO 18-Sep-2020)

	Study A2201						All NSCLC subjects						All solid tumor subjects					
	Asian N=84		Caucasian N=281		Others N=8		Asian N=104		Caucasian N=342		Others N=12		Asian N=132		Caucasian N=431		Others N=17	
Preferred Term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Number of subjects with at least one event	**83 (98.8)**	**63 (75.0)**	**276 (98.2)**	**187 (66.5)**	**8 (100)**	**6 (75.0)**	**103 (99.0)**	**78 (75.0)**	**337 (98.5)**	**230 (67.3)**	**12 (100)**	**8 (66.7)**	**131 (99.2)**	**88 (66.7)**	**425 (98.6)**	**275 (63.8)**	**17 (100)**	**11 (64.7)**
Oedema peripheral	32 (38.1)	6 (7.1)	166 (59.1)	30 (10.7)	4 (50.0)	0	39 (37.5)	7 (6.7)	196 (57.3)	32 (9.4)	4 (33.3)	0	50 (37.9)	7 (5.3)	225 (52.2)	32 (7.4)	5 (29.4)	0
Nausea	44 (52.4)	1 (1.2)	123 (43.8)	8 (2.8)	1 (12.5)	0	54 (51.9)	2 (1.9)	155 (45.3)	10 (2.9)	2 (16.7)	0	67 (50.8)	3 (2.3)	194 (45.0)	12 (2.8)	5 (29.4)	0
Dyspnoea	8 (9.5)	2 (2.4)	78 (27.8)	23 (8.2)	1 (12.5)	0	10 (9.6)	2 (1.9)	101 (29.5)	28 (8.2)	1 (8.3)	0	12 (9.1)	2 (1.5)	112 (26.0)	29 (6.7)	2 (11.8)	0
Vomiting	32 (38.1)	2 (2.4)	72 (25.6)	7 (2.5)	1 (12.5)	0	38 (36.5)	2 (1.9)	95 (27.8)	10 (2.9)	2 (16.7)	0	50 (37.9)	3 (2.3)	122 (28.3)	13 (3.0)	3 (17.6)	0
Blood creatinine increased	31 (36.9)	0	65 (23.1)	0	3 (37.5)	0	38 (36.5)	0	75 (21.9)	0	3 (25.0)	0	46 (34.8)	1 (0.8)	85 (19.7)	0	3 (17.6)	0
Fatigue	19 (22.6)	2 (2.4)	61 (21.7)	14 (5.0)	3 (37.5)	0	24 (23.1)	2 (1.9)	78 (22.8)	16 (4.7)	4 (33.3)	0	29 (22.0)	2 (1.5)	104 (24.1)	20 (4.6)	5 (29.4)	1 (5.9)
Decreased appetite	28 (33.3)	2 (2.4)	51 (18.1)	2 (0.7)	0	0	34 (32.7)	2 (1.9)	67 (19.6)	4 (1.2)	0	0	42 (31.8)	2 (1.5)	88 (20.4)	5 (1.2)	2 (11.8)	0
Cough	10 (11.9)	0	49 (17.4)	1 (0.4)	2 (25.0)	1 (12.5)	14 (13.5)	0	59 (17.3)	1 (0.3)	2 (16.7)	1 (8.3)	16 (12.1)	0	65 (15.1)	1 (0.2)	2 (11.8)	1 (5.9)

Diarrhoea	17 (20.2)	2 (2.4)	48 (17.1)	0	1 (12.5)	0	19 (18.3)	2 (1.9)	64 (18.7)	2 (0.6)	2 (16.7)	0	24 (18.2)	2 (1.5)	85 (19.7)	3 (0.7)	3 (17.6)	0
Constipation	23 (27.4)	2 (2.4)	46 (16.4)	1 (0.4)	0	0	25 (24.0)	2 (1.9)	57 (16.7)	2 (0.6)	0	0	28 (21.2)	2 (1.5)	74 (17.2)	4 (0.9)	0	0
Back pain	18 (21.4)	2 (2.4)	43 (15.3)	1 (0.4)	0	0	21 (20.2)	3 (2.9)	53 (15.5)	1 (0.3)	0	0	22 (16.7)	3 (2.3)	63 (14.6)	4 (0.9)	0	0
Pyrexia	19 (22.6)	1 (1.2)	32 (11.4)	2 (0.7)	1 (12.5)	0	20 (19.2)	1 (1.0)	42 (12.3)	4 (1.2)	1 (8.3)	0	24 (18.2)	1 (0.8)	52 (12.1)	5 (1.2)	1 (5.9)	0
Alanine aminotransferase increased	18 (21.4)	7 (8.3)	31 (11.0)	16 (5.7)	2 (25.0)	1 (12.5)	21 (20.2)	7 (6.7)	38 (11.1)	21 (6.1)	2 (16.7)	1 (8.3)	25 (18.9)	8 (6.1)	47 (10.9)	23 (5.3)	2 (11.8)	1 (5.9)
Hyperbilirubinaemia	0	0	0	0	2 (25.0)	1 (12.5)	0	0	1 (0.3)	0	2 (16.7)	1 (8.3)	0	0	2 (0.5)	0	2 (11.8)	1 (5.9)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
Others includes Native American, Black, Unknown and Other.
MedDRA version 23.1, CTCAE version 4.03.

The AESI groups and the respective PTs with incidences ≥ 10% in both subgroups and also with a difference ≥ 5% between subgroups are presented in the sequence of Asian vs. Caucasian subgroups, respectively: Hepatotoxicity-grouped AESIs: 44.0% vs. 26.0%; ALT increased: 21.4% vs. 11.0%; Renal dysfunction-grouped AESIs: 38.1% vs. 24.6%; Blood creatinine increased: 36.9% vs. 23.1%. All the QTc interval prolongation AESIs were observed in Caucasians.

ECOG performance status (DCO 18-Sep-2020)

As per protocol, 28.7% subjects and 71.0% subjects had baseline ECOG-PS of 0 and 1, respectively. The incidence of Nausea and Dyspnoea was higher in ECOG-PS ≥ 1 subgroup; the incidence of Fatigue was higher in the ECOG-PS=0 subgroup; for other most common AEs, the incidence was similar between subgroups (differences < 10% subjects). In Study A2201, there were no differences in the incidence of AESI between ECOG-PS subgroups (ECOG-PS = 0 and ECOG-PS ≥ 1). No AESI groups or PTs were observed with incidences ≥ 10% in both subgroups and also with a difference ≥ 5% between subgroups.

Region (Asia/Pacific vs. Europe/Middle East vs. Americas) (DCO 18-Sep-2020)

The majority of enrolled subjects were from Europe/Middle East (66.5%), the rest were from Asia/Pacific (21.2%) or Americas (12.3%) (data not shown). There were no difference of overall AE incidence by geographic region. Among the most common AEs, the incidence of Nausea was similar (difference < 10% subjects) across geographic region subgroups; the incidence of Fatigue was similar between Asia/Pacific and Europe/Middle East which was lower than Americas; the incidences of Vomiting, Blood creatinine increased and Decreased appetite were similar for Europe/Middle East and Americas which was lower than Asia/Pacific; the incidences of Oedema peripheral and Dyspnoea were similar for Europe/Middle East and Americas which was higher than Asia/Pacific subgroup.

The AESI groups and the respective PTs with incidences ≥ 10% in all subgroups and also with a difference ≥ 5% across subgroups are presented below in the sequence of Asia/Pacific vs. Europe/Middle East vs. Americas, respectively: Hepatotoxicity-grouped AESI: 44.3% vs. 25.0% vs. 37.0%; ALT increased: 20.3% vs. 10.5% vs. 19.6%.

Subjects with hepatic impairment (DCO 18-Sep-2020)

In study A2201, there were no differences in overall AE incidences by hepatic impairment based on baseline laboratory values. For the most common AEs, there were no differences between normal and mild hepatic impairment subgroups (difference < 10% subjects) with the exception of Dyspnea (higher in mild hepatic impairment subgroups).

The AESI groups and the respective PTs with incidences ≥ 10% in all subgroups and also with a difference ≥ 5% across subgroups are presented below in the sequence of Normal vs. Mild impairment, respectively: Hepatotoxicity-grouped AESI: 28.7% vs. 47.4%; ALT: 12.3% vs. 26.3%.

Subjects with renal impairment (DCO 18-Sep-2020)

Based on laboratory values at baseline, subjects were categorized as subgroups with normal, mild and moderate renal impairment. In Study A2201, there were no differences of overall AE incidences by renal impairment. For the most common AEs, all were similar (difference < 10% subjects) among subgroups, with the exceptions of Nausea, Blood creatinine increased and Decreased appetite (highest rate in moderate subgroup, then the mild subgroup and last in the normal subgroup). The AESI groups and the respective PTs with incidences ≥ 10% in all subgroups and also with a difference ≥ 5% across subgroups are presented in the sequence of Normal vs. Mild vs. Moderate, respectively: Renal dysfunction-grouped AESI: 14.6% vs. 27.1% vs. 48.3%; Blood creatinine increased: 13.1% vs. 25.8% vs. 47.1%.

Pregnancy
Based on findings from animal studies and its mechanism of action, capmatinib can cause foetal harm when administered to a pregnant woman due to its foetotoxicity and teratogenicity. There are no data from the use of capmatinib in pregnant women. Oral administration of capmatinib to pregnant rats and rabbits during organogenesis resulted in fetotoxicity and teratogenicity. Reduced foetal weights and increased incidences of foetal malformations were observed in rats and rabbits following prenatal exposure to capmatinib at or below the exposure in humans at the MRHD of 400 mg b.i.d. based on AUC.

Lactation
It is not known if capmatinib is transferred into human milk after administration of capmatinib. There is insufficient information on the excretion of capmatinib or its metabolites in animal milk. There are no data on the effects of capmatinib on the breastfed child or on milk production.

Overdose

No information about overdose has been generated in support of this application. In case of suspected overdose, subjects should be closely monitored for signs or symptoms of adverse drug reactions, and general supportive measures and symptomatic treatment should be initiated.

Drug abuse

A possible risk of misuse or dependence on capmatinib is not anticipated based on its mechanism of action. While no clinical studies have been carried out to specifically investigate abuse potential with capmatinib, no evidence has emerged that would suggest a potential for abuse or dependence. Given the pattern of side effects, and given the absence of effects that could lead to dependence, there is no known potential for abuse of capmatinib.

Withdrawal and rebound

No information about withdrawal and rebound has been generated in support of this application. No studies have been conducted to assess withdrawal and rebound effects.

Effects on ability to drive or operate machinery or impairment of mental ability

With regard to Nausea, Vomiting, Visual impairment, fatigue events (coded as Fatigue and Asthenia), and dizziness events (coded as Dizziness, Vertigo and Vertigo positional), the majority of these AEs were of grade 1/2 severity across the 3 datasets. These AEs were not considered to have any significant impact on the ability to drive and use machines. Among the AEs of Nausea, Vomiting and fatigue events, the majority were grade 1 events and did not require dose adjustment. The incidence of dizziness events appeared to be similar to the prevalence in the general adult and elderly population, further confounded by higher number of subjects with baseline brain metastasis. After applying Bradford Hill's criteria in medical analysis of dizziness events in Study A2201, Novartis concluded that the dizziness events were not causally related to capmatinib. The incidence of Visual impairment was minor (< 1% subjects), all

of which were grade 1/2 in severity. All of the subjects with Visual impairment in Study A2201 had baseline medical histories (meningioma, vertigo, headache, brain metastasis and prior radiotherapy to brain), which were considered as confounding factors for visual impairment.

2.6.6.7. Safety related to drug-drug interactions and other interactions

Capmatinib with PPI (rabeprazole): Study A2101 was a Phase I, open-label, single-center, 2-period, single-sequence study to assess the effect of rabeprazole on the PK of a single dose of capmatinib in healthy subjects.

Capmatinib administered after treatment with rabeprazole versus capmatinib administered alone resulted in Geometric mean ratios (GMRs) and two-sided 90% CIs for AUCinf, AUClast, and Cmax of 0.748 (0.637 to 0.878), 0.746 (0.660 to 0.844), and 0.625 (0.533 to 0.734), respectively. Lower AUCinf, AUClast, and Cmax occurred when capmatinib was administered after treatment with rabeprazole compared to capmatinib administered alone (25.2%, 25.4%, and 37.5% lower, respectively). The median Tmax difference for capmatinib (administered after treatment with rabeprazole - capmatinib administered alone) was 0.01 h. Therefore, PPIs should be used with caution.

Capmatinib with CYP3A inhibitor (itraconazole) and CYP3A inducer (rifampicin): Study A2102 was an open-label, single-center, Phase I study with a 2-arm (cohort) fixed sequence, 2-period, DDI study to assess the effect of itraconazole and rifampicin on the PK of a single dose of capmatinib in healthy subjects. Results indicate that caution should be exercised during concomitant use with strong CYP3A inhibitors and moderate CYP3A inducers.

Capmatinib with food: Two studies (Study X2107 in healthy subjects and Study A2108 in cancer subjects) had evaluated effect of capmatinib with food. The results from both studies indicate that food does not alter capmatinib bioavailability to a clinically meaningful extent; therefore, capmatinib may be administered with or without food.

2.6.6.8. Discontinuation due to adverse events

As of the DCO (30-Aug-2021), 65 (17.4%) subjects had AEs that led to permanent discontinuation of study treatment. The most common (> 2% subjects) AE that resulted in permanent discontinuation of study treatment was oedema peripheral. The findings were consistent between MET mutant subjects and all A2201 subjects.

Table 80. Adverse events irrespective of study drug relationship leading to permanent discontinuation of study treatment by preferred term and maximum grade with an incidence ≥0.5% (all grades in any population) (Safety set) – Study A2201 - DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
- Total	31 (19.4)	22 (13.8)	65 (17.4)	41 (11.0)
Oedema peripheral	4 (2.5)	3 (1.9)	8 (2.1)	4 (1.1)
Pneumonitis	3 (1.9)	1 (0.6)	6 (1.6)	1 (0.3)
Fatigue	1 (0.6)	1 (0.6)	5 (1.3)	3 (0.8)
Alanine aminotransferase increased	2 (1.3)	1 (0.6)	3 (0.8)	2 (0.5)
Aspartate aminotransferase increased	2 (1.3)	0	3 (0.8)	1 (0.3)
Blood creatinine increased	2 (1.3)	0	3 (0.8)	0
Nausea	0	0	3 (0.8)	1 (0.3)
Pneumonia	1 (0.6)	1 (0.6)	3 (0.8)	3 (0.8)
Vomiting	0	0	3 (0.8)	1 (0.3)
Blood bilirubin increased	2 (1.3)	0	2 (0.5)	0
Breast cancer	1 (0.6)	1 (0.6)	2 (0.5)	2 (0.5)
Cardiac failure	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.3)
General physical health deterioration	0	0	2 (0.5)	2 (0.5)
Interstitial lung disease	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Lipase increased	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Organising pneumonia	1 (0.6)	1 (0.6)	2 (0.5)	1 (0.3)
Pleural effusion	0	0	2 (0.5)	1 (0.3)
Adenocarcinoma gastric	1 (0.6)	0	1 (0.3)	0
Amylase increased	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Cardiopulmonary failure	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Drug-induced liver injury	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Hepatic function abnormal	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Hypoacusis	1 (0.6)	0	1 (0.3)	0
Hypotension	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Metastatic malignant melanoma	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Oedema genital	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Respiratory distress	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Respiratory failure	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Septic shock	1 (0.6)	1 (0.6)	1 (0.3)	1 (0.3)
Urticaria	1 (0.6)	0	1 (0.3)	0

AEs were graded according to the CTCAE V4.03. MedDRA version 24.0 was used.

As of the DCO (30-Aug-2021), 230 subjects (61.7%) had ≥ 1 AE that required dose adjustment and/or interruption of the study treatment. The most common (> 5% subjects) AEs leading to dose adjustment and/or interruption were: oedema peripheral, blood creatinine increased, nausea, vomiting, ALT increased, and lipase increased. The findings were consistent between the MET mutant subjects and all A2201 subjects except (≥5% difference in frequency) all grades oedema peripheral (23.1% in MET mutant subjects vs 15.5% in all A2201 subjects).

Table 81. Adverse events irrespective of study drug relationship requiring dose adjustment and/or interruption by preferred term and maximum grade with an incidence ≥1% (all grades in any population) (Safety set) – Study A2201 - DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)
- Total	105 (65.6)	80 (50.0)	230 (61.7)	163 (43.7)
Oedema peripheral	37 (23.1)	17 (10.6)	58 (15.5)	27 (7.2)
Blood creatinine increased	20 (12.5)	1 (0.6)	34 (9.1)	1 (0.3)
Nausea	15 (9.4)	1 (0.6)	28 (7.5)	4 (1.1)
Vomiting	10 (6.3)	1 (0.6)	25 (6.7)	4 (1.1)
Alanine aminotransferase increased	13 (8.1)	12 (7.5)	22 (5.9)	20 (5.4)
Lipase increased	13 (8.1)	13 (8.1)	21 (5.6)	21 (5.6)
Dyspnoea	6 (3.8)	2 (1.3)	17 (4.6)	6 (1.6)
Pneumonia	6 (3.8)	2 (1.3)	16 (4.3)	8 (2.1)
Amylase increased	9 (5.6)	8 (5.0)	15 (4.0)	13 (3.5)
Aspartate aminotransferase increased	6 (3.8)	5 (3.1)	14 (3.8)	10 (2.7)
Fatigue	6 (3.8)	4 (2.5)	12 (3.2)	9 (2.4)
Decreased appetite	6 (3.8)	1 (0.6)	11 (2.9)	3 (0.8)
Asthenia	7 (4.4)	5 (3.1)	10 (2.7)	7 (1.9)
Blood bilirubin increased	4 (2.5)	0	8 (2.1)	0
Diarrhoea	3 (1.9)	0	8 (2.1)	1 (0.3)
Pleural effusion	4 (2.5)	1 (0.6)	7 (1.9)	2 (0.5)
Generalised oedema	5 (3.1)	5 (3.1)	6 (1.6)	6 (1.6)
Pyrexia	3 (1.9)	1 (0.6)	6 (1.6)	1 (0.3)
Cellulitis	3 (1.9)	2 (1.3)	5 (1.3)	2 (0.5)
Dysphagia	0	0	5 (1.3)	0
General physical health deterioration	1 (0.6)	0	5 (1.3)	4 (1.1)
Platelet count decreased	3 (1.9)	1 (0.6)	5 (1.3)	3 (0.8)
Abdominal pain	1 (0.6)	1 (0.6)	4 (1.1)	2 (0.5)
Abdominal pain upper	4 (2.5)	0	4 (1.1)	0
Anaemia	2 (1.3)	2 (1.3)	4 (1.1)	4 (1.1)
Dyspepsia	2 (1.3)	0	4 (1.1)	0
Gamma-glutamyltransferase increased	3 (1.9)	2 (1.3)	4 (1.1)	2 (0.5)
Pneumonitis	3 (1.9)	0	4 (1.1)	0
Lymphocyte count decreased	3 (1.9)	3 (1.9)	3 (0.8)	3 (0.8)
Malaise	2 (1.3)	1 (0.6)	3 (0.8)	2 (0.5)
Oedema	3 (1.9)	2 (1.3)	3 (0.8)	2 (0.5)
Transaminases increased	2 (1.3)	2 (1.3)	3 (0.8)	2 (0.5)
Capillary leak syndrome	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Face oedema	2 (1.3)	0	2 (0.5)	0
Hyperbilirubinaemia	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.3)
Hypoacusis	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Neutrophil count decreased	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Scrotal oedema	2 (1.3)	0	2 (0.5)	0
Skin lesion	2 (1.3)	0	2 (0.5)	0
Thrombocytopenia	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)

AEs were graded according to the CTCAE V4.03. MedDRA version 24.0 was used.

Table 82. Adverse events irrespective of study drug relationship requiring dose adjustment by preferred term and maximum grade with an incidence ≥1% (all grades in any population) (Safety set) – Study A2201. - DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)
- Total	60 (37.5)	18 (11.3)	98 (26.3)	28 (7.5)
Oedema peripheral	26 (16.3)	8 (5.0)	34 (9.1)	11 (2.9)
Alanine aminotransferase increased	8 (5.0)	3 (1.9)	12 (3.2)	4 (1.1)
Blood creatinine increased	6 (3.8)	0	8 (2.1)	0
Nausea	4 (2.5)	0	7 (1.9)	0
Decreased appetite	3 (1.9)	0	5 (1.3)	0
Fatigue	4 (2.5)	2 (1.3)	5 (1.3)	3 (0.8)
Vomiting	3 (1.9)	0	5 (1.3)	0
Generalised oedema	2 (1.3)	2 (1.3)	3 (0.8)	2 (0.5)
Amylase increased	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.3)
Capillary leak syndrome	2 (1.3)	0	2 (0.5)	0
Lipase increased	2 (1.3)	0	2 (0.5)	0
Oedema	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.3)

AEs were graded according to the CTCAE V4.03. MedDRA version 24.0 was used.

Table 83. Adverse events irrespective of study drug relationship requiring dose interruption by preferred term and maximum grade with an incidence ≥1% (all grades in any population) (Safety set) – Study A2201. DCO: 30-Aug-2021

	All MET mutant subjects N=160		All A2201 subjects N=373	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)
- Total	96 (60.0)	71 (44.4)	211 (56.6)	148 (39.7)
Oedema peripheral	23 (14.4)	11 (6.9)	41 (11.0)	19 (5.1)
Blood creatinine increased	18 (11.3)	1 (0.6)	31 (8.3)	1 (0.3)
Nausea	13 (8.1)	1 (0.6)	23 (6.2)	4 (1.1)
Lipase increased	13 (8.1)	13 (8.1)	21 (5.6)	21 (5.6)
Vomiting	8 (5.0)	1 (0.6)	21 (5.6)	4 (1.1)
Alanine aminotransferase increased	10 (6.3)	9 (5.6)	18 (4.8)	16 (4.3)
Dyspnoea	6 (3.8)	2 (1.3)	17 (4.6)	6 (1.6)
Pneumonia	6 (3.8)	2 (1.3)	16 (4.3)	8 (2.1)
Amylase increased	8 (5.0)	7 (4.4)	14 (3.8)	12 (3.2)
Aspartate aminotransferase increased	5 (3.1)	4 (2.5)	12 (3.2)	9 (2.4)
Asthenia	7 (4.4)	5 (3.1)	9 (2.4)	7 (1.9)
Blood bilirubin increased	4 (2.5)	0	8 (2.1)	0
Diarrhoea	2 (1.3)	0	7 (1.9)	1 (0.3)
Fatigue	2 (1.3)	2 (1.3)	7 (1.9)	6 (1.6)
Pleural effusion	4 (2.5)	1 (0.6)	7 (1.9)	2 (0.5)
Decreased appetite	3 (1.9)	1 (0.6)	6 (1.6)	3 (0.8)
Pyrexia	3 (1.9)	1 (0.6)	6 (1.6)	1 (0.3)
Cellulitis	3 (1.9)	2 (1.3)	5 (1.3)	2 (0.5)
Dysphagia	0	0	5 (1.3)	0
General physical health deterioration	1 (0.6)	0	5 (1.3)	4 (1.1)
Abdominal pain	1 (0.6)	1 (0.6)	4 (1.1)	2 (0.5)
Abdominal pain upper	4 (2.5)	0	4 (1.1)	0
Anaemia	2 (1.3)	2 (1.3)	4 (1.1)	4 (1.1)
Dyspepsia	2 (1.3)	0	4 (1.1)	0
Gamma-glutamyltransferase increased	3 (1.9)	2 (1.3)	4 (1.1)	2 (0.5)
Generalised oedema	3 (1.9)	3 (1.9)	4 (1.1)	4 (1.1)
Lymphocyte count decreased	3 (1.9)	3 (1.9)	3 (0.8)	3 (0.8)
Malaise	2 (1.3)	0	3 (0.8)	1 (0.3)
Platelet count decreased	2 (1.3)	1 (0.6)	3 (0.8)	2 (0.5)
Pneumonitis	2 (1.3)	0	3 (0.8)	0
Capillary leak syndrome	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Hyperbilirubinaemia	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.3)
Hypoacusis	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Neutrophil count decreased	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Oedema	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.3)
Scrotal oedema	2 (1.3)	0	2 (0.5)	0
Thrombocytopenia	2 (1.3)	2 (1.3)	2 (0.5)	2 (0.5)
Face oedema	2 (1.3)	0	2 (0.5)	0

AEs were graded according to the CTCAE V4.03. MedDRA version 24.0 was used.

2.6.6.9. Post marketing experience

Capmatinib received approval in the US on 6-May-2020 and, in Japan on 29-Jun-2020, and in Hong Kong on 26-Feb-2021. Between 06-May-2020 and 12-Dec-2020 (DCO for the latest DSUR), based on the number of units sold, patient exposure to capmatinib (Tabrecta) is estimated to be approximately 185 patient treatment years. Review of the safety data received during the reporting periods and the available cumulative experience to date did not identify any new or changing safety signal with capmatinib. Review of AEs and SAEs reported to the applicant's pharmacovigilance database from post-marketing settings cumulatively until 05-Nov-2021 identified no new safety information of impact on the current benefit-risk assessment of capmatinib.

2.6.7. Discussion on clinical safety

The main safety dataset to support this MAA consists of safety data from Study A2201, which included 373 NSCLC subjects (Cohorts 1-7), 160 of which are MET-mutated NSCLC patients (cohorts 5b and 7 [treatment naïve]; Cohorts 4 and 6 [pre-treated patients]). Additional supportive data were provided from 6 pooled studies: study A2201 (main study), study X1101 (Japanese only), study X2102 (dose escalation), study A2103 (DDI), study A2105 (DDI), and study A2108 (dose escalation). These data were grouped into 2 separate datasets of subjects treated with capmatinib monotherapy at the RD of 400 mg b.i.d tablet or the equivalent RD of 600 mg b.i.d. capsule: all NSCLC subjects (n=458), all solid tumour subjects (N=580). Safety data from these 2 pools are considered generally supportive, although the NSCLC pool is considered more relevant in the context of the intended indication.

The single arm, non-controlled design hampers causality assessment, as in oncology there might be a pronounced overlapping of symptoms with the underlying malignant disease. In addition, the causality assessment will be affected by the current knowledge (or lack thereof) of the medicine's safety profile, which will likely introduce bias.

The supportive data sets of the "all NSCLC subjects" and "All solid tumour subjects" subsets may lack sensitivity to show differences with study A2201. The study population of study A2201 is also included in these data sets and provided 81% (all NSCLC) and 64% (all solid tumour types) of the supportive data sets. No new safety signals were identified by presenting the safety data for non-overlapping A2201, NSCLC, and solid tumour cohorts. The type of AEs observed were similar.

Overall, the size of the capmatinib safety database in NSCLC is small (n=373), particularly for the MET-mutated NSCLC patient subset (n=160). In addition, the uncontrolled, open-label nature of the main study and the limited long-term exposure adds some limitations for an adequate characterization of the safety profile of capmatinib in the intended indication.

A total of 373 NSCLC patients (including 160 MET-mutated patients) were included in the Safety Population. At the DCO of 30 August 2021, amongst MET mutant subjects, 21 subjects (13.1%) were ongoing in the treatment phase and the primary reasons (> 10%) for discontinuation were disease progression (55.0%); amongst all A2201 subjects, 23 subjects (6.2%) were ongoing in the treatment phase and the primary reasons (> 10%) for discontinuation remained similar to those reported in the original submission, i.e., disease progression (64.1%) and AEs (17.7%).

In the MET-mutated cohorts, the median exposure duration was 34.9 months (range: 0.4-195.7), which was longer than the duration for the MET-amplified cohorts (12.1 months (range: 0.6-281.0) and the overall NSCLC population (17.9 months (range: 0.4-281.0). Approximately 60% (n=94) of patients in the MET-mutated cohort had at least 24 weeks of exposure, with 39.4% (n=63) having at least 48 weeks. Although exposure duration has increased with the updated data, the number of patients with 48 or longer weeks of exposure remains low. Therefore, the additional 11 months of

follow-up did not lead to significantly longer exposure and long-term exposure to capmatinib is, therefore, still rather limited.

The most common adverse reactions are peripheral oedema (67.5%), nausea (44.4%), fatigue (34.4%), vomiting (25.0%), dyspnoea (22.5%), decreased appetite (21.3%) and back pain (20.6%). The most common grade 3 or 4 adverse reactions are peripheral oedema (14.4%), fatigue (8.1%) and dyspnoea (6.9%).

Serious adverse reactions were reported in 35 patients (21.9%) who received Tabrecta. Serious adverse reactions in >2% of patients included dyspnoea (5.6%), ILD/pneumonitis (5.0%), cellulitis (3.1%) and peripheral oedema (2.5%).

Dose interruptions were reported in 50.6% of patients. Adverse reactions requiring dose interruption included peripheral oedema (15.0%), blood creatinine increased (11.3%), lipase increased (8.1%), nausea (8.1%), ALT increased (6.3%), fatigue (5.6%), amylase increased (5.0%), vomiting (5.0%), dyspnoea (3.8%), blood bilirubin increased (3.1%) and AST increased (3.1%).

Dose reductions were reported in 30.6% of patients. Adverse reactions requiring dose reductions included peripheral oedema (16.3%), ALT increased (5.0%), blood creatinine increased (3.8%), fatigue (3.1%) and nausea (2.5%).

Permanent discontinuation was reported in 11.9% of patients. The most frequent adverse reactions leading to permanent discontinuation of Tabrecta were ILD/pneumonitis (3.8%), peripheral oedema (2.5%), ALT increased (1.3%), AST increased (1.3%), blood bilirubin increased (1.3%), blood creatinine increased (1.3%), lipase increased (1.3%), amylase increased (0.6%), fatigue (0.6%) and urticaria (0.6%).

AESIs

The following AEs were predefined as AESIs, based on current knowledge on the pharmacological class, mode of action and non-clinical/clinical findings: ILD/pneumonitis, Hepatotoxicity, Renal dysfunction, CNS toxicity, Pancreatitis, Photosensitivity, Teratogenicity, DDI with strong CYP3A inducers, and QTc interval prolongation.

These adverse events have been included in the RMP as either important identified risks (i.e., hepatotoxicity, ILD/pneumonitis, pancreatitis) or as important potential risks (the rest of AESIs, except for Teratogenicity, DDI with strong CYP3A inducers, and QTc prolongation).

In the overall population from study A2201 (most recent DCO 30-Aug-2021), AESIs were reported in ≥ 10% of patients were: hepatotoxicity (31.9%), renal dysfunction (28.4%), CNS toxicity (18.8%), and pancreatitis (14.2%). In general, a small increase in frequencies (from original submission) is observed across most AESIs, indicating that their incidence increases with increasing exposure. The majority of the grade 3-4 AESIs had resolved at the time of the most recent data cut-off.

ILD/pneumonitis, which can be fatal, has occurred in patients treated with Tabrecta. Prompt investigation should be performed in any patient with new or worsening of pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough, fever). Tabrecta should be immediately withheld in patients with suspected ILD/pneumonitis and permanently discontinued if no other potential causes of ILD/pneumonitis are identified.

Transaminase elevations have occurred in patients treated with Tabrecta. Liver function tests (including ALT, AST and total bilirubin) should be performed prior to the start of treatment, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop transaminase or bilirubin elevations. Based on the severity of the adverse reaction, temporarily withhold, dose reduce, or permanently discontinue Tabrecta.

Elevations in amylase and lipase levels have occurred in patients treated with Tabrecta. Amylase and lipase should be monitored at baseline and regularly during treatment with Tabrecta. Based on the severity of the adverse reaction, temporarily withhold, dose reduce, or permanently discontinue Tabrecta (see sections 4.2, 4.4 and 4.8 of the SmPC).

Based on findings from animal studies, there is a potential risk of photosensitivity reactions with Tabrecta. In Study GEOMETRY mono 1, it was recommended that patients limit direct ultraviolet exposure during treatment with Tabrecta and adopt the following protective measures: use of sunscreen on exposed parts of the body, wearing of protective clothing and sunglasses. These measures should be continued for at least 7 days after the last dose (see section 4.4 and 5.3 of the SmPC).

Regarding CNS toxicity, in the preclinical tests, capmatinib appears to have a high CNS toxicity in rats, but not in monkeys, which is somewhat concerning.

In the original submission, the reported incidence of the AESI CNS toxicity-grouped in humans appear to increase with age. The reported frequency for < 65 years, 65-75 years and >75 years were 13.6%, 19.1% and 26.7%, respectively. Most AEs were of grade 1-2. The CNS function reserve in elderly is impaired compared to the younger patients, which might be an explanation for the observed increased frequency. AE grade 3-4 rate was low, so it appears that the impact of the CNS AEs was low. These data do not provide a strong signal for clinically relevant CNS toxicity. However, the provided safety database remains to be limited, particularly for the long term, which preclude a definite conclusion.

In this context, it is agreed with the applicant that the inclusion of AEs concerning psychiatric disorders, sensory abnormalities, and decreases in consciousness does not improve the identification of CNS toxicity in the specific elderly NSCLC population in study A2201. The observed AEs occurred in low frequencies, were usually low in grade and did not lead to discontinuations. The occurrence of these AEs were confounded by the age of the population and the underlying disease. Even though the additional review did not raise new concerns about CNS toxicity, this safety risk should be further characterised post-marketing. Available non-clinical evidence does not allow to exclude the possibility that the observed CNS effects in rats could be related to the pharmacological mode of action of capmatinib. However, it is noted that the lesions were observed only in one species and occurred at exposure levels somewhat above the anticipated clinical exposure, which provides some reassurance about the clinical safety. It is also noted that capmatinib is indicated for the treatment of advanced or metastatic NSCLC which is a life-threatening condition, thus possible long-term neurological effects may be less relevant in such patients and currently no safety concerns were raised. Due to the uncertainties of the current safety database being limited in number of patients and follow-up and based on non-comparative studies, the risk of CNS toxicity will be further monitored post-marketing, including a comparative analysis of the AESI of 'CNS toxicity' in the phase III randomised, controlled study CINC280A2301 in which docetaxel will be used as the control. CNS toxicity is included as a safety concern in the RMP

Swallowing difficulties

Capmatinib tablets have a large tablet size, which rises a concern due to potential swallowing problems in the proposed target population of advanced NSCLC because this population is predisposed to such problems due to the presence of coexisting factors like cervical/tracheal lymphadenopathy, etc.

The safety database of study A2201 included 19 (5.1%) subjects with reported dysphagia (all grades). Almost all events were reported in patients with contributing factors (e.g. metastatic cervical/paratracheal lymphadenopathy, laryngeal oedema, among others). It is acknowledged that in the absence of controlled data a definite correlation cannot be made between the tablet size and swallowing difficulties. However, these data do warrant concerns about the swallowing difficulties in this predisposed population. Given that dysphagia was reported less frequently in the cohorts without fasting restrictions, a statement

has been included in section 4.2 of the SmPC, recommending patients with swallowing difficulties to take Tabrecta with food.

Changes in laboratory parameters

Most of the changes in laboratory parameters were grade 1-2. Grade 3-4 AEs identified in the context of the predefined AESIs (e.g., ALT/AST/GGT increased-hepatotoxicity; lipase/amylase increase-pancreatitis).

Special populations

Age: Of the 160 patients with METex14 skipping alterations in the GEOMETRY mono-1 study who received 400 mg capmatinib twice daily, 85% were 65 years or older, and 4.4% were 85 years or older. The occurrence of grade ≥3 events increased with age. Treatment-related serious events were more frequent in patients aged ≥65 to <75 years (22%) and those aged ≥85 years (28.6%) when compared to those patients aged ≥75 to <85 years (8.5%) and patients younger than 65 years (8.3%), although this comparison is limited by the small sample size in patients aged ≥85 years.

MET mutant and amplified population: When looking at the different MET aberration cohorts, the safety profile appears to be similar between MET mutated patients, MET amplified patients, and all A2201 patients, except for oedema peripheral and blood creatinine increased. Oedema peripheral and blood creatinine increased occurred more often in MET mutated patients. Oedema peripheral was observed in 65.0% (13.8% Grade 3-4) in the MET mutant patients, 46.5% (7.0% Grade 3-4) in the MET amplified patients, and 54.4% (9.9% Grade 3-4) in all A2201 patients. Blood creatinine increased was observed in 33.8% (0.6% Grade 3-4) in the MET mutant patients, 22.1% (0% Grade 3-4) in the MET amplified patients, and 27.1% (0.3% Grade 3-4) in all A2201 patients. It is noted that the patients in the MET mutated cohorts were older and had a longer exposure than patients in the MET amplified cohorts, which could partly explain the differences. While the overall safety profile of MET mutated and MET amplified patients appears to be similar, the lack of a control group, do not allow to soundly conclude on this aspect at this time.

Based on findings from animal studies and its mechanism of action, capmatinib is suspected to cause congenital malformations when administered during pregnancy. Tabrecta should not be used during pregnancy unless the clinical condition of the woman requires treatment with capmatinib. Sexually-active women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with Tabrecta and for at least 7 days after the last dose.

Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with Tabrecta and for at least 7 days after the last dose.

The pregnancy status of women of childbearing potential should be verified prior to starting treatment with Tabrecta. A risk to the breast-fed infant cannot be excluded. Because of the potential for serious adverse reactions in breast fed infants, breast feeding should be discontinued during treatment with Tabrecta and for at least 7 days after the last dose. No human fertility data on capmatinib are available.

Pooled data

Data in the NSCLC pool were consistent and generally supportive of the findings in the main study, since this study contributed with 2/3 of patients included in this pool.

Contextualisation

The currently provided safety data is obtained in a single arm trial and lacks contextualization with currently approved treatments.

The safety profile of capmatinib is mainly characterised by the adverse event profile as shown by other TKIs. The adverse event profile includes nausea, vomiting, peripheral oedema, interstitial lung disease, hepatoxicity, pancreatitis and blood creatinine increased.

This safety profile differs from the known safety profile of other approved treatments for METmut NSCLC. The safety profile of these approved products are characterised with bone marrow suppression (chemotherapy) and/or immunological events (immunotherapy). As such, capmatinib may provide an additional treatment option.

No relevant studies have been conducted however Tabrecta is expected to have no or negligible influence on the ability to drive and use machines (see section 4.7 of the SmPC).

There is limited experience with overdose in clinical studies with Tabrecta. Patients should be closely monitored for signs or symptoms of adverse drug reactions, and general supportive measures and symptomatic treatment should be initiated in cases of suspected overdose (see section 4.9 of the SmPC).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics (see section on Adverse drug reactions).

2.6.8. Conclusions on the clinical safety

There are several limitations for the characterization of the safety prolife of capmatinib in the intended indication.

Overall, the size of the safety database is still small, comprising a dataset of 373 NSCLC patients, which include 160 MET-mut patients, i.e., the target population. In addition, the duration of the follow-up in the MET-mut patients provided with the most recent DCO was 39.4% (n=63) patients with a minimum exposure of at least 48 weeks.

Further, the safety database mainly derives from 1 single, uncontrolled, on-going. Phase II study. The single arm trial hamper causality assessment and contextualisation of the safety profile in the current treatment armamentarium.

As a result, there are some uncertainties related to these limitations.

The overall incidence of adverse events (98.4%), severe AEs (70.2%) and SAEs (53.1%) was high. The overall safety profile of capmatinib is characterised by the known safety profile of TKIs, including nausea, vomiting, hepatoxicity, pneumonitis/ILD, pancreatitis and blood creatinine increased. Clarification on several safety issues is still pending.

The safety profile is associated with frequent dose interruptions/adjustment and start of additional treatments to warrant the drug tolerability and the patient’s safety. Nevertheless, with these measures, the safety profile appeared to be manageable with a reported frequency of treatment discontinuations of 17% (original submission), and the frequency of toxic deaths of 1% (original submission). Overall, this safety profile could be acceptable for an anti-cancer drug in advanced NSCLC if an outstanding benefit can be anticipated.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 84: List of safety concerns

List of safety concerns	
Important identified risks	Hepatotoxicity Interstitial lung disease/pneumonitis Pancreatitis
Important potential risks	Renal dysfunction Photosensitivity CNS toxicity
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities are planned. Routine pharmacovigilance activities are considered sufficient to address the risks of Tabrecta.

2.7.3. Risk minimisation measures

Table 85: Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Important identified risks		
Hepatotoxicity	**Routine risk minimization measures** SmPC Section 4.2, Section 4.4, Section 4.8 PL Section 2, PL Section 4 SmPC Section 4.2 includes detailed guidance for withholding or permanent discontinuation of doses. SmPC Section 4.4 includes guidance on monitoring and management of hepatic effects. Also includes guidelines for withholding or permanent discontinuation of doses. PL Section 2 provides guidance on blood tests prior to start of treatment and during the treatment with Tabrecta to check the liver function. PL Section 4 includes guidance on monitoring and management of very common side effects of liver problems. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Interstitial lung disease/pneumonitis	**Routine risk minimization measures** SmPC Section 4.2, Section 4.4, Section 4.8 PL Section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC Section 4.2 prompts for permanent discontinuation in case of treatment related interstitial lung disease/pneumonitis of any grade. SmPC Section 4.4 includes guidance on monitoring and management of Interstitial lung disease/pneumonitis. Also includes guidelines for withholding or permanent discontinuation of doses. PL Section 4 includes guidance on monitoring and management of common side effects of pneumonitis, interstitial lung disease. **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** None
Pancreatitis	**Routine risk minimization measures** SmPC Section 4.2, Section 4.4, Section 4.8 PL Section 2, PL Section 4 SmPC Section 4.2 includes guidance on temporarily withhold, dose reduce, or permanently discontinue treatment, depending on severity. SmPC Section 4.4 includes guidance on regular monitoring of pancreatic enzymes (amylase and lipase) prior and during treatment with capmatinib. PL Section 2 provides guidance on blood tests prior to start of treatment and during the treatment with Tabrecta to check the pancreatic function. PL Section 4 includes guidance on monitoring and management of uncommon side effects of acute pancreatitis. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risks		
Renal dysfunction	**Routine risk minimization measures** SmPC Section 4.2, Section 4.8, Section 5.2 PL Section 4 SmPC Section 4.2 includes detailed guidance for temporarily withholding treatment until recovery to baseline serum creatinine grade or permanent discontinuation of treatment. PL Section 4 includes guidance on monitoring and management of side effects which may be a sign of renal problems. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Comparative safety analysis from phase 3 study CINC280A2301 to be presented in PSURs, after each key analysis. **Additional pharmacovigilance activities:** None
Photosensitivity	**Routine risk minimization measures** SmPC Section 4.4, Section 5.3 PL Section 4 SmPC Section 4.4 includes guidance on monitoring and management of photosensitivity. PL Section 4 includes guidance on monitoring and management of possible common side effects of skin infection. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
CNS toxicity	**Routine risk minimization measures** SmPC Section 5.3 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Comparative safety analysis from phase 3 study CINC280A2301 to be presented in PSURs, after each key analysis. **Additional pharmacovigilance activities:** None
Missing information		
None		

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 06.05.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

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

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that

this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.>

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final agreed indication is: "Tabrecta as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum based chemotherapy".

The aim of treatment in subjects with advanced NSCLC is to prolong survival and mitigate symptoms, as cure is not expected due to the extension of disease.

3.1.2. Available therapies and unmet medical need

Second line options in advanced NSCLC with no established molecular driver such as EGFR, BRAF, ALK, ROS-1, RET, NTRK fusion, etc are checkpoint inhibitors and docetaxel/ramicirumab-docetaxel with ORRs of 14% -23%, DORs of 16-19 months (longer for pembrolizumab in PD-L1 $\geq$ 1%; KEYNOTE-010), and OS medians of about 12 months, and platinum doublets for patients who received checkpoint-inhibitor monotherapy first line.

Approximately 3% of NSCLCs harbour MET exon 14 (METex14) skipping alterations, leading to a truncated MET receptor lacking the exon 14 encoded sequences (Network Tcgar, Nature, 2014). Deletion (i.e., skipping of exon 14) results in oncogenic activation of MET by expression of a truncated receptor with increased stability, as well as augmented and prolonged signalling capability, seemingly turning MET into an oncogenic driver (Cortot 2017). Currently, there is no available treatment option that specifically targets advanced NSCLC harboring METex14 skipping alterations. The median OS of METex14 NSCLC patients who never received a MET inhibitor was reported to be in the range of 8 to 11 months (Awad 2019, Wolf 2018). Furthermore, METex14 skipping alterations have been found to be most frequently reported in elderly patients (Schrock 2016, Awad 2019).

In December 2021, CHMP issued a positive opinion recommending the marketing authorization of Tepmetko, intended for the treatment of patients with NSCLC harbouring alterations leading to METex14 skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

3.1.3. Main clinical studies

The pivotal registration **Study CINC280A2201** (also called **GEOMETRY mono-1**) is a global, prospective, multi-cohort, non-randomized, open-label Phase II study with a Bayesian interim monitoring designed to evaluate the efficacy and safety of single-agent capmatinib 400mg bid in subjects with EGFR wild type (wt), ALK negative rearrangement, advanced (stage IIIB or IV) NSCLC harbouring METex14 skipping alterations (detected by RT-PCR), and/or MET amplification (detected by FISH). The study enrolled 373 subjects distributed in a total of 9 cohorts (1a, 1b, 2, 3, 4, 5a, 5b, 6, and 7), defined by the type of MET dysregulation and previous systemic treatment status. Expansion Cohorts 6 and 7 were

added to generate additional supportive safety and efficacy data in the pre-treated and treatment-naïve settings, respectively, in consideration of feedback from HA consultations.

Primary efficacy data supporting the indication is restricted to 2 cohorts that include NSCLC patients with METex14 skipping mutations who were pre-treated with 1 or 2 lines of prior systemic therapy for advanced stage disease, i.e. Cohort 4 (n=69) and Cohort 6 (n=39).The current data cut-off date is 30 August 2021. The efficacy data supporting the finally agreed indication come from Cohorts 4 and 6.

Primary endpoint is overall response rate (ORR), defined as the proportion of subjects with a best overall response (BOR) defined as complete response or partial response (CR+PR) by BIRC assessment per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Secondary endpoints include DOR by BIRC, ORR and DOR per RECIST 1.1 by investigator assessment, time to response (TTR), DCR, PFS, and OS.

3.2. Favourable effects

A total of 100 pre-treated NSCLC patients with a METex14 skipping mutation were included in cohort 4 (n=69) and cohort 6 (n=31).

Primary endpoint: ORR by BIRC

- In Cohort 4, the **ORR** was **40.6%** (95% CI: 28.9, 53.1), with 1 confirmed CR (1.4%). **Median DoR** was **9.72 months** (95% CI: 5.55, 12.98).
- In Cohort 6, the **ORR** was **51.6%** (95% CI: 33.1, 69.8), all confirmed PR. **Median DoR** was **9.05 months** (95% CI: 4.17, NE)
- Pooled analysis: **ORR** was **44.0%** (95% CI: 34.1, 54.3), with one confirmed CR. **Median DoR** was **9.72 months** (95% CI: 5.62, 12.98) as assessed by BIRC.

Other secondary endpoints:

- The median PFS by BIRC was 5.42 months (95% CI: 4.17, 6.97) for cohort 4, and 6.93 months (95% CI: 4.17, 13.34) for cohort 6.
- Median OS was 13.57 months (95% CI: 8.61, 22.24), for Cohort 4 and 24.28 (13.54, NE) for Cohort 6.

Consistent results were observed for the secondary endpoints as per investigator assessment.

Subgroup findings were generally consistent with the overall treatment effect.

3.3. Uncertainties and limitations about favourable effects

The evidence provided to support this indication is limited to antitumoral responses (estimated magnitude and duration of responses) coming from a non-controlled, non-randomised, open label phase II trial.

The lack of randomisation and the open-label design mean that a risk for both selection and assessment bias cannot be totally ruled out. An independent central review committee for antitumor assessment and determination of METex14 status by a central laboratory were put in place, which reduce the risk of bias. However, still an overestimation of the antitumor effect by the selection of a favourable subset of METmut patient by the investigators and/or by the assessment of tumour responses cannot be completely ruled out. Moreover, it is noted that PFS and OS results are difficult to interpret in a single arm trial. The MAH is therefore recommended to provide the results of the ongoing RCT (NCT04427072).

The study population is more homogeneous than what is expected in the target population (e.g. no patients with ECOG PS2 or unstable brain metastases included in the study). The study population has been properly reflected in Section 5.1 of the SmPC.

It is claimed that patients with METmut NSCLC are more advanced (elderly, with higher burden of disease) and have a worse prognosis and poor treatment outcomes compared to the general NSCLC population, but with the (limited) quality of the available evidence this cannot be firmly concluded at present. Though it can be reasonably ruled out that this is a marker of good prognosis and/or predictive of good response to SOC.

The large tablet size may contribute to problems with swallowing. A recommendation for patients with swallowing difficulties to take Tabrecta with food has been included in the SmPC.

3.4. Unfavourable effects

The main safety dataset to support this MAA consists of safety data from Study A2201, which includes a total of 373 patients with advanced NSCLC, including 160 patients (42%) with NSCLC harbouring a MET mutation.

In Study A2201 (DCO 30 August 2021), 70.2% subjects experiencing Grade ≥ 3 AEs, 53.1% experienced SAEs.

The median duration of treatment with capmatinib in the MET mutant patients was 34.9 months (range: 0.4-195.7); 39.4% of the patients were exposed for at least 48 weeks. The **most common AE** by PT, irrespective of study drug relationship, were oedema peripheral, nausea, vomiting, blood creatinine increased, dyspnoea, fatigue, and decreased appetite. The most common **Grade ≥ 3 AEs** were oedema peripheral (9.9%), dyspnoea (7.0%) and ALT increased (7.0%). Most common **treatment-related Grade ≥ 3 AEs** were peripheral oedema (9.1%), ALT increased (5.6%), lipase increased (6.4%).

The most **common SAEs** were similar, i.e. dyspnoea, pneumonia, pleural effusion, general physical health deterioration, and vomiting.

Overall, 17.4% of patients experienced an **AE leading to permanent treatment discontinuation**, the most frequent ones were oedema peripheral, and pneumonitis; 11.0% of patients experienced a Grade ≥ 3 AEs that led to the permanent discontinuation of study treatment.

The proportion of patients with any **AEs leading to dose interruption/reductions** was 61.7%, most often due to oedema peripheral, blood creatinine increased, nausea, vomiting, ALT increased, and lipase increased.

Twelve (3.2%) patients experienced **AEs that led to death**, 4 of them considered by the investigators as related to capmatinib.

AE PTs: oedema peripheral and blood creatinine increased occurred more often in MET mutated patients. Oedema peripheral was observed in 65.0% (13.8% Grade 3-4) in the MET mutant patients, 46.5% (7.0% Grade 3-4) in the MET amplified patients, and 54.4% (9.9% Grade 3-4) in all A2201 patients. Blood creatinine increased was observed in 33.8% (0.6% Grade 3-4) in the MET mutant patients, 22.1% (0% Grade 3-4) in the MET amplified patients, and 27.1% (0.3% Grade 3-4) in all A2201 patients.

Capmatinib appears to be less tolerated in elderly patients (age 75-85), who had more dose adjustments and treatment interruptions than younger patients (<65), 73% vs. 53%, respectively. Side effects such as renal dysfunction (18.4% vs 41.7%) and the AESI CNS toxicity (13.6% vs 26.7%) were also more frequent in elderly patients.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainty concerns the size of the capmatinib safety database in NSCLC, which is small (n=373), particularly for the patient subset of patients harbouring METex14 skipping alterations (n=160). In addition, the uncontrolled, open-label nature of the main study adds some limitations for an adequate characterization of the safety profile of capmatinib in the intended indication and makes the AE causality assessment challenging.

Renal dysfunction was reported by almost a third of patients treated with capmatinib, most of them due to increased blood creatinine events, which is related to the inhibition of MATE1 and MATE2k renal transporters exerted by capmatinib. This issue is particularly relevant for the elderly population, which represents a large proportion of the intended population and are per se vulnerable to experiencing renal toxicity.

The preclinical test showed a worrisome potential high CNS toxicity in rodents in the thalamic region. Although the currently provided safety data do not reveal a strong signal for the AESI CNS toxicity, long term follow-up is limited. Renal dysfunction and CNS toxicity have been included in the RMP as a "potential identified risks" and both will be monitored in the post-marketing setting under routine pharmacovigilance activities.

3.6. Effects Table

Table 86: Effects Table for Tabrecta (capmatinib) in the treatment of adults patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation (data cut-off: 30 Aug 2021)

	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
ORR per BIRC	Pre-treated (pooled; n=100)	%	44.0% (95% CI: 34.1, 54.3)		With certainty a drug effect. ORR is a surrogate endpoint and thus not a direct measure of clinical benefit There is no control arm included in study A2201, and cross-study comparisons are necessary for contextualization of the results.
DoR per BIRC	Pre-treated (pooled)	months	9.72 (95% CI: 5.62, 12.98)		Addresses clinical relevance of responses but is limited by relevance only for responders. There is no control arm included in study A2201, and cross-study comparisons are necessary for contextualization of the results.

	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Unfavourable Effects					
General Safety profile (DCO 30 Aug 2021)			All patients (n= 373)	MET-mutated (n=160)	The provided data are the overall number of adverse event.
	AE overall		98.4%	98.8%	
	≥G3 AEs		70.2%	73.1%	Safety data obtained in an open label single arm trial, which hampers causality assessment
	SAEs		53.1%	49.4%	
	SAEs leading to death		3.2%	3.8%	
	AE leading to treatment discontinuation		17.4%	19.4%	
	AE leading to dose reductions		26.3%	37.5%	
	AE leading to dose interruptions		56.6%	60.0%	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, high tumour responses rates and durable responses as assessed by BIRC are observed across the two cohorts relevant for the sought indication (cohort 4 & 6). Point estimates of antitumor responses and median DoR in the two cohorts of treatment experienced population were 40.6% and 9.72 months for Cohort 4 and 51.6% and 9.05 months for cohort 6, respectively, by BIRC review.

However, it is important to note is that there are approved first and second-line therapies available, and the contextualization of the results is based on indirect comparisons. In addition, for this population (i.e. METex14 skipping mutated NSCLC) the natural course of the disease and the response to therapy is not well known.

For the **second- or subsequent line setting** (i.e. pre-treated cohorts), capmatinib showed compelling anti-tumour activity (high number of relatively durable responses) which can be considered as sufficient when compared to docetaxel, the benchmark treatment at the time of the study conduct. These data are considered robust as replication of the ORR and DoR data in the 2L+ population has been shown in two independent cohorts and are supported by the DoR and ORR results in the first line setting. With the approval of immunotherapies in the first line setting, docetaxel is the benchmark therapy in the 2L setting.

The overall size of the safety database for capmatinib includes 160 MET-mutated patients and patients from the post-approval setting.

The overall incidence of Grade ≥3 adverse events (70.2%) and serious AEs (53.1%) is high. The safety profile of capmatinib is mainly characterised by the adverse event profile as shown by other TKIs, and includes nausea, vomiting, peripheral oedema, interstitial lung disease, hepatotoxicity, pancreatitis and blood creatinine increased.

The tablet size is large and a recommendation for patients with swallowing difficulties, i.e. to take Tabrecta with food, is included in section 4.2 of the SmPC. The safety profile differs from other approved

treatments for unselected NSCLC, with bone marrow suppression (chemotherapy) and/or immunological events (e.g., immunotherapy) as key AEs.

Further, treatment with capmatinib was associated with a high number of treatment adjustment/interruptions and need for additional therapy in order to manage these events. Nevertheless, with these measures, the safety profile appeared to be generally manageable with a reported frequency of treatment discontinuations of 17%. Overall, these reported frequencies are acceptable for a medicine in advanced NSCLC and with the differential safety profile as compared to SoC, capmatinib provides an alternative treatment option for patients.

3.7.2. Balance of benefits and risks

Despite available therapies, advanced NSCLC has a poor prognosis and there remains a need for new treatment options. Precision medicine plays an important role in the treatment of NSCLC, evident by the number of targeted therapies approved.

The results in terms of anti-tumour activity and relatively durable responses can be considered clinically relevant for the second- and subsequent line settings, considering that available non-targeted therapies show modest anti-tumour activity and it is likely that capmatinib will show improved efficacy over those therapies and similar to the recently approved MET inhibitor tepotinib.

The product has a different mode of action and offers a different safety profile compared to non-targeted approved treatments. The product was associated with a high number of dose adjustments in the clinical program indicating that its use should be carefully monitored. Nevertheless, the number of treatment discontinuation and toxic deaths are considered acceptable in the proposed indication. Since the toxicity is acceptable and based on the tumour-activity observed so far, it is likely that capmatinib will show improved efficacy over available therapies that only showed modest anti-tumour activity in the second line treatments, the benefits outweigh the risks in the second- or subsequent-line settings.

3.7.3. Additional considerations on the benefit-risk balance

The ORR and DoR for the previously treated population exceed the reported mDoR for docetaxel in the 2L+ treatment, the benchmark therapy when immunotherapy became available in the first line setting. Based on the available evidence, the B/R of capmatinib for the 2L+ population is considered positive. Regarding the comprehensiveness of the overall data presented, a full approval for the 2L+ setting is considered appropriate because:

- Replication of the ORR and DoR data in the 2L+ population has been shown in two independent cohorts (in total 100 patients). Also, the reported ORR and DoR for the 2L+ clearly exceed the reported ORR and DoR of docetaxel in this setting, providing reassurance that the capmatinib data very likely results in PFS and OS benefit in the 2L+ population.
- The ORR and DoR results in the 2L+ setting are supported by the DoR and ORR results in the first line setting. This leads to an efficacy database of n=160 patients, with n=100 patients included in the proposed target population of 2L+ NSCLC.
- Safety is different from other non-targeted treatments and is deemed sufficiently characterised as the overall safety database includes 373 patients.

In addition, the applicant will provide final results from the ongoing A2201 phase II study as well as from the ongoing phase III randomized clinical in the second line (study A2301), when available, in the context of post-approval recommendations.

3.8. Conclusions

The overall benefit/risk balance of Tabrecta is positive, subject to the conditions stated in section 'Recommendations'.

Divergent position is 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 Tabrecta is favourable in the following indication:

Tabrecta as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

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

Refer to Appendix on new active substance (NAS).

Divergent position

Divergent position to the majority recommendation is appended to this report.

5. Appendices

5.1. CHMP AR on New Active Substance (NAS) dated 22 April 2022

5.2. Divergent position to the majority recommendation

DIVERGENT POSITION DATED 22 April 2022

DIVERGENT POSITION DATED 22 April 2022

TABRECTA EMEA/H/C/004845/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of TABRECTA indicated for the following indication:

TABRECTA as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

The reason for divergent opinion was the following:

Tabrecta has shown activity across different lines in a single-arm trial (SAT – GEOMETRY mono-1 study). Since the application is based on a SAT, evidence is less robust than in a randomised controlled trial (RCT) and selection bias cannot be ruled out. Even though the ORR and DOR results from Cohort 4 of the GEOMETRY mono-1 study were replicated in Cohort 6, these endpoints are not surrogate endpoints for OS and PFS in NSCLC. Available treatment options have established efficacy and safety in RCTs and shown OS and PFS benefits. Confirmatory data from a randomized clinical trial are considered necessary to address the above uncertainties. Thus, the dossier is not considered suitable for full approval. A conditional marketing approval (CMA) would have been a more appropriate regulatory pathway for Tabrecta.

CHMP Members expressing a divergent opinion:

Thalia Marie Estrup Blicher

Christophe Focke

Christian Gartner

Armando Genazzani

Ilko Getov

Andrea Laslop

Outi Mäki-Ikola

Jan Müller-Berghaus

Robert Porszasz

Ingrid Wang

Martina Weise