CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213591Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	213591
Priority or Standard	Priority
Submit Date(s)	December 10, 2019
Received Date(s)	December 10, 2019
PDUFA Goal Date	August 10, 2020
Division/Office	DO2/OOD
Review Completion Date	April 30, 2020
Established Name	Capmatinib
(Proposed) Trade Name	Tabrecta
Pharmacologic Class	Kinase inhibitor
Code name	INC280, formerly known as INCB28060
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	Tablets: 150 mg and 200 mg
Dosing Regimen	400 mg orally twice daily with or without food
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a mesenchymal-epithelial transition (MET) exon 14 skipping mutation as detected by an FDA-approved test
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
b.i.d.	twice daily
BIRC	Blinded Independent Review Committee
BOR	best overall response
CI	confidence interval
CNS	central nervous system
CR	complete response
CRS	case retrieval strategy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug induced liver injury
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
FAS	full analysis set
FCT	film coated tablet
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
GCN	gene copy number
GGT	gamma-glutamyltransferase
HGF	hepatocyte growth factor
IND	Investigational New Drug
IDE	investigational device exemption
IO	Immunotherapy
LFT	liver function test
MATE1	Multidrug and toxin extrusion proteins-1

MATE2k	Multidrug and toxin extrusion proteins-2k
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NE	not estimable
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
OATP	Organic anion-transporting polypetide
OCT	Organic cation transporter
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand – 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPI	proton-pump inhibitor
PR	partial response
PT	preferred term
PS	performance status
QLQ	quality of life questionnaire
RDI	relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase II dose
RT-PCR	reverse transcription polymerase chain reaction
RWE	real-world evidence
SAE	serious adverse event
SD	stable disease
SOC	system organ class
TMB	tumor mutation burden
TPS	tumor proportion score
TTR	time to response
ULN	upper limit of normal

1 Executive Summary

1.1. Product Introduction

Capmatinib (INC280) is an orally bioavailable adenosine triphosphate (ATP) competitive kinase inhibitor that targets the mesenchymal-epithelial transition factor (MET) receptor tyrosine kinase, including the mutated variant produced by MET exon 14 skipping. Capmatinib is not currently approved in the United States or any other part of the world. The proposed dosing regimen for capmatinib is 400 mg orally twice daily (BID) on a continuous schedule. Novartis' proposed indication for capmatinib is "treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a mesenchymal-epithelial transition (MET) exon 14 skipping mutation as detected by an FDA-approved test".

1.2. Conclusions on the Substantial Evidence of Effectiveness

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The recommendation for accelerated approval according to 21 CFR 314.510 Subpart H is based on results from two cohorts of patients with metastatic NSCLC whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping mutation who received capmatinib 400 mg BID in a multicenter, non-randomized, multi-cohort study (Study A2201, GEOMETRY mono-1). The demonstrated overall response rates (ORR) per Blinded Independent Review Committee (BIRC) of 68% with a median DOR of 12.6 months in 28 treatment-naïve patients and 41% with a median duration of response (DOR) of 9.7 months in 69 patients who had disease progression after one or two prior therapies are considered clinically meaningful when considering the intended patient population, patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping mutation.

For NSCLC, ORR may be considered an endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable (Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics). Based on these findings, FDA expects that capmatinib will have, as described in section 505(d) of the Act, "the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Metastatic non-small cell lung cancer (NSCLC) is a fatal, incurable disease, with a 5-year survival rate of <10%. Mutations that lead to mesenchymal-epithelial transition (MET) exon 14 skipping have been identified as an oncogenic driver mutation in NSCLC and have been reported to be present in 2-4% of all NSCLC tumors. In comparison to some other subpopulations of patients with targetable genomic tumor aberrations (i.e., EGFR mutation, ALK rearrangement), patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping tend to be older (median age around 70 years), similar to the general population of patients with NSCLC. Based on the limited data available for review, there is no indication that patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping have a higher response rate when treated with platinum-based chemotherapy and/or immunotherapy compared to the general population of patients with NSCLC. There is no targeted therapy approved specifically for the treatment of patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping.

Capmatinib is a kinase inhibitor that targets MET, including the mutated variant produced by MET exon 14 skipping. The proposed dosing regimen is 400 mg orally twice daily (BID) with or without food. Novartis' proposed indication for capmatinib is "treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a mesenchymal-epithelial transition (MET) exon 14 skipping mutation as detected by an FDA-approved test."

The primary efficacy analysis population for this review comprises 97 patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping treated with capmatinib 400 mg BID in the multi-cohort clinical trial, Study A2201 (GEOMETRY mono-1), including 69 patients with disease progression following one or two prior therapies ("previously treated") and 28 treatment-naïve patients. The confirmed overall response rate (ORR) assessed by blinded independent central review (BICR) in treatment-naïve patients was 68% (95% CI: 48, 84) and the median duration of response was 12.6 months (95% CI: 5.5, 25.3), with 47% of the 19 responders having observed DOR of ≥ 12 months. In the previously treated population, the confirmed ORR per BICR was 41% (95% CI: 29, 53) and the median duration of response was 9.7 months (95% CI: 5.5, 13.0), with 32% of the 28 responders having observed DOR of ≥ 12 months. These response rates, coupled with the durability of responses observed, are consistent with a clinically meaningful benefit when considering the intended patient population.

Capmatinib appears to have an acceptable safety profile when assessed in the context of a life-threatening disease. The most common (≥ 20%) adverse reactions were peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite. Permanent discontinuation of capmatinib due to adverse reactions occurred in 16% of patients; the most frequent adverse reactions leading to permanent discontinuation were peripheral edema (1.8%), pneumonitis (1.8%), and fatigue (1.5%). Safety issues identified as significant and serious during the NDA review were interstitial lung disease/pneumonitis and hepatotoxicity. These safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).

A supplemental premarket application (sPMA) for a companion diagnostic (FoundationOne®CDx) was submitted by Foundation Medicine Inc. for contemporaneous review with this NDA.

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for accelerated approval. Capmatinib has a favorable benefit-risk profile in the indicated population based on the high response rate and durable responses observed in a patient population with a life-threatening disease and an unmet medical need. Given the relatively limited duration of follow-up for both cohorts and the small number of treatment-naïve patients in the primary efficacy analysis population for this application, the current data are considered adequate to support accelerated approval rather than regular approval. Due to the relatively low incidence of MET mutations leading to exon 14 skipping in NSCLC, a randomized trial in this patient population is not feasible. To verify the clinical benefit of capmatinib in patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping, additional data will be obtained from the clinical trial which supported this approval, Study A2201.

The review team's regulatory recommendation is to grant capmatinib accelerated approval for the following indication: "For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer death in the U.S., with 80% to 85% of all lung cancer cases identified as non-small cell lung cancer (NSCLC). • Mutations that lead to mesenchymal-epithelial transition (MET) exon 14 skipping have been identified as an oncogenic molecular driver mutation in NSCLC and have been reported in approximately 2-4% of NSCLC tumors. • The 5-year survival rate for patients with metastatic NSCLC is <10%. There is no randomized trial data available regarding survival specifically for patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. • Based on the limited data available for review, there is no indication that patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping have a higher response rate when treated with platinum-based chemotherapy and/or immunotherapy compared to the general population of patients with NSCLC.	Metastatic NSCLC with mutation leading to MET exon 14 skipping is a life-threatening disease with poor survival. NSCLC with mutations that lead to MET exon 14 skipping is a rare subset of NSCLC; approximately 2-4% of NSCLC tumors have a mutation that leads to MET exon 14 skipping.
Current Treatment Options	• There is no targeted therapy approved specifically for the treatment of patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. • Current treatment options for patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping are the same as those used for NSCLC without a specific driver mutation identified. • For treatment-naïve patients this includes platinum-based chemotherapy and/or anti-PD-(L)1 antibody. The highest ORRs, ranging from 46% to 58%, have been reported for platinum-based chemotherapy plus pembrolizumab (regardless of histology) and platinum-based chemotherapy plus atezolizumab with or without bevacizumab (for non-squamous NSCLC) with median durations of response of approximately 11 months. • For patients with progression of disease following platinum-based chemotherapy, treatment options include chemotherapy (single agent or docetaxel in combination with ramucirumab) associated with ORR 6-23% with median durations of response in the	There is an unmet medical need for patients with treatment-naïve and previously treated metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. This conclusion is based on the observed response rates, durations of response, and overall survival reported for therapies currently used in clinical practice for the treatment of this patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	range of 4 to 9 months or single agent anti-PD(L)1 antibody if not received in the first-line setting, associated with ORR 14-20% with median durations of response in the range of 16 to 17 months.	
Benefit	• The primary efficacy data supporting this NDA are from patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping enrolled in two cohorts, Cohort 4 ("previously treated", with progression following one or two prior therapies) and Cohort 5b ("treatment-naïve", no prior therapy for metastatic NSCLC), of Study A2201 (GEOMETRY mono-1), a multicenter, non-randomized, open-label, multi-cohort study in patients with NSCLC with MET mutation and/or amplification. • Among the 28 treatment-naïve patients, confirmed ORR per BIRC was 68% (95% CI 48, 84) with median DOR of 12.6 months (95% CI 5.5, 25.3). • Among the 69 patients who had received previous treatment, confirmed ORR per BIRC was 41% (95% CI: 29, 53) with median DOR of 9.7 months (95% CI 5.5, 13.0). • Given the relatively limited duration of follow-up for both cohorts and the small number of treatment-naïve patients in the primary efficacy analysis population for this application, the current data are considered adequate to support accelerated approval rather than regular approval. • A limitation of single arm trials is the potential for known and unknown patient selection bias.	The submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed ORRs, along with the observed duration of responses, are clinically meaningful when considering the intended patient population. The magnitude of the ORR in the treatment-naïve population was sufficiently large to overcome the uncertainty related to the small sample size in the context of an accelerated approval. Additional data to verify the clinical benefit of capmatinib will be obtained from the clinical trial which supported this approval, Study A2201. Based on the demographic and baseline disease characteristics for the patients in the primary efficacy analysis population for this application, this population is comparable to the overall U.S. target population. Therefore, the benefit demonstrated in Study A2201 is expected to extend to the post-market setting.
Risk and Risk Management	• The safety database for this NDA includes 541 patients with solid tumors who were treated with capmatinib at the recommended dose, including 334 patients from Study A2201. The data used to inform labeling includes the 334 patients with metastatic NSCLC who received capmatinib 400 mg orally twice daily in Study A2201. The safety	The observed safety profile of capmatinib is acceptable when assessed in the context of the treatment of this life-threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	data in this NDA is adequate to assess safety with reference to the overall U.S. target population. • Permanent discontinuation of capmatinib due to adverse reactions occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of capmatinib were peripheral edema (1.8%), pneumonitis (1.8%), and fatigue (1.5%). • While 54% of patients had capmatinib dosing interrupted for adverse reaction, dose reductions due to adverse reactions occurred in 23% of patients. • The most common adverse events (AEs) were peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite. • Safety issues considered significant and serious enough to warrant inclusion in the Warnings and Precautions section of the USPI for capmatinib are interstitial lung disease / pneumonitis and hepatotoxicity. Based on in vitro data, a warning regarding phototoxicity was also included in labeling. • In a single arm study such as Study A2201, a direct comparison of capmatinib-associated toxicity versus toxicity observed with current standard of care therapy (chemotherapy, anti-PD(L)1 antibodies) is not possible.	Although capmatinib can cause severe/serious toxicities, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. Capmatinib will be prescribed by oncologists who know how to monitor, identify, and manage such toxicities. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			x	Patient reported outcome (PRO)	Section 8.1.2
			□	Observer reported outcome (ObsRO)	Not applicable
			□	Clinician reported outcome (ClinRO)	Not applicable
			□	Performance outcome (PerfO)	Not applicable
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			Not applicable
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			Not applicable
	□	Natural history studies			Not applicable
	□	Patient preference studies (e.g., submitted studies or scientific publications)			Not applicable
	□	Other: (Please specify)			Not applicable
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Cross-Disciplinary Team Leader
Erin Larkins, M.D.

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Non-small cell lung cancer accounts for approximately 85% of all lung cancer cases and, in 2018, there were an estimated 154,050 lung cancer related deaths in the United States (US) (Siegel et al 2018). MET mutations leading to exon 14 skipping have been reported in approximately 2% to 4% of NSCLC population (TCGA 2014, Frampton et al 2015, Paik et al 2015, Awad et al 2016, Campbell et al 2016, Schrock et al 2016, Tong et al 2016).

MET mutations are an established and independent oncogenic driver in advanced NSCLC. Molecular epidemiology data indicate that MET mutations are mutually exclusive with other molecular drivers, while there is a degree of overlap with MET amplifications (which still needs to be quantified more precisely) (TCGA 2014, Schrock et al 2016). Thus MET mutations leading to exon 14 skipping have been identified as an actionable target in NSCLC (Kong-Beltran et al 2006, Pasquine and Giaccone 2018), and multiple MET inhibitors have been tested in nonclinical and clinical studies (Jenkins et al 2015, Liu et al 2016, Mendenhall and Goldman 2015, Paik et al 2015, Waqar et al 2015, Drilon et al 2016).

Patients with tumors that have MET-dysregulation (including MET mutations) have poor prognosis compared to the unselected NSCLC patient population (Dimou et al 2014, Guo et al 2014, Landi et al 2017, Awad et al 2019). In the most recent series of MET-mutated NSCLC in advanced stage (n=148), the overall survival (OS) measured since the diagnosis of stage IV was only 8.1 months for patients not treated with a therapy targeting MET (Awad et al 2019). Such patients tend to be elderly (~more than 10 years older than other subpopulations of patients with NSCLC), making this population clinically challenging, primarily due to comorbidities and overall frailty, which limits the use of currently available treatment options, ultimately impacting on the prognosis of this subset of patients (Awad et al 2019, Drilon et al 2017).

Currently, there is no approved targeted therapy for patients with MET exon 14 skipping mutated NSCLC.

The FDA's Assessment:

FDA agrees with Novartis' analysis of condition, as described.

The Applicant's Position:

Capmatinib (INC280) is an oral highly selective, reversible and potent inhibitor of MET receptor tyrosine kinase. It is highly specific for MET with ≥ 1,000-fold selectivity over more than 400 other human kinases or mutant kinase variants. Potent inhibitory activity has also been observed in cell-based assays that measure MET-mediated signal transduction, as well as MET-dependent cell proliferation, survival, and migration.

Clinical efficacy has been reported with capmatinib in patients whose tumors harbor MET alterations such as mutations that lead to exon 14 skipping, including in treatment-naïve patients which confirms the value of MET exon 14 skipping mutations in predicting the response to targeted therapies directed against MET (Frampton et al 2015, Schuler et al 2016, Wolf et al 2017, Wolf et al 2018, Wolf et al 2019).

Collectively, the data suggest that capmatinib possesses potent in vitro and in vivo biological and pharmacologic activities, and further support its clinical development as an effective targeted oral treatment primarily in NSCLC harboring MET exon 14 skipping mutations (as detected by an FDA approved test).

The efficacy evaluation for this submission is mainly based on the primary efficacy analysis of MET mutated NSCLC cohorts (pretreated Cohort 4 and treatment naïve Cohort 5b) who have completed at least 6 cycles/18 weeks of treatment or have discontinued treatment earlier, in support of the filing for capmatinib in this population.

The FDA's Assessment:
The Applicant's positions stated above are not relevant to this section of the review.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

There are currently no approved targeted therapies for patients with MET exon 14 skipping mutated NSCLC. Current treatment options for advanced NSCLC patients are systemic chemotherapy and immunotherapy (IO) (Gettinger and Lynch 2011, Hirsch et al 2016, Morgensztern and Herbst 2016, Reck et al 2016), unless a patient has a "druggable molecular driver" and is a candidate for targeted therapy (NCCN Guidelines v5 2019).

Treatment options for patients with advanced NSCLC with no established molecular driver (e.g. ALK gene rearrangements, ROS1 rearrangements, sensitizing EGFR mutations and BRAF V600E point mutations) are based on IO, either as monotherapy or in combination with platinum doublets (Planchard et al 2018, NCCN Guidelines v5 2019).

Combination Chemo-immunotherapy
A combination of IO with platinum doublets may be considered as first-line treatment irrespective of tumor PD-L1 expression (Garon et al 2015, Reck et al 2016, Gandhi et al 2018, Hellmann et al 2018, Paz-Ares et al 2018, Sheela et al 2018, Socinski et al 2018, Heinhuis et al 2019).

Single Agent Immunotherapy
Single-agent IO is considered as first-line treatment in patients whose tumors have programmed death-ligand-1 (PD-L1) expression > 50%, and in pretreated patients irrespective of PD-L1 expression (Planchard et al 2018, NCCN Guidelines v5 2019).
The PD1 inhibitor pembrolizumab is also approved by FDA as monotherapy for first-line treatment of advanced NSCLC whose tumors express PD-L1 (tumor proportion score (TPS) ≥ 1%).

Systemic Chemotherapy (without IO)
Alternatively, systemic chemotherapy without the addition of IO is an option for patients not eligible for single agent or combination IO therapy (Fosella et al 2000, Schiller et al 2002, Lilenbaum et al 2005, Pujol et al 2005, Scagliotti et al 2008, Scagliotti et al 2014, Malhotra et al 2017).

Outcomes of treatment with platinum-doublet chemotherapy remain poor for locally advanced/metastatic NSCLC in the treatment-naïve setting, with a median Progression free survival (PFS) of 5-7 months and overall survival (OS) of 10-16 months (Scagliotti et al 2008, Ciuleanu et al 2009, Ettinger et al 2010, Paz-Ares et al 2012).

Single-agent chemotherapy is mostly used in the pretreated setting; however, it can be an option also in first-line patients who are ineligible for single-agent IO or IO/chemotherapy combination regimens (Fosella et al 2000, Schiller et al 2002, Lilenbaum et al 2005, Pujol et al 2005, Scagliotti et al 2008, Scagliotti et al 2014, Malhotra et al 2017).

Targeted Therapies
Treatment options for patients with advanced NSCLC whose tumors have an established molecular driver are primarily based on targeted therapy. Compared to systemic chemotherapy, treatment with an appropriate targeted therapy is associated with improved PFS and quality of life (QoL) in patients with advanced NSCLC (Solomon et al 2014, Yang et al 2016, Brahmer et al 2017, Hida et al 2017, Reck 2018).

Since patients with NSCLC tumors harboring molecular drivers derive limited benefit from IO treatment with IO-based therapies is recommended only after exhausting the benefit from the appropriate targeted therapy (Mazieres 2019). Alternatively, such patients are also candidates

for chemotherapy after exhausting targeted therapy options (NCCN Guidelines v5 2019, Hirsch et al 2016).

The FDA's Assessment:
FDA agrees with Novartis' analysis of current treatment options for metastatic NSCLC.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Capmatinib (INC280) is not currently registered (or approved) in the US or any other part of the world.

The FDA's Assessment:
FDA agrees that capmatinib is not approved in the United States or any other part of the world.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
Novartis submitted IND 116,691 on 09-Nov-2012 to FDA to support the investigation of capmatinib in MET-dependent advanced solid tumors. The "Study May Proceed" letter was issued on 10-Dec-2012. IND 116,691 now serves as the "anchor IND" for capmatinib. Novartis subsequently submitted IND 124,033 on 29-Jan-2015 to FDA to support the investigation of capmatinib in EGFR wt, advanced NSCLC with Study A2201. The "Study May Proceed" letter was issued on 27-Feb-2015. All further interactions related to Study A2201 were conducted under IND 124,033.

The regulatory input received from FDA on various occasions at different interactions is summarized in Table 1.

Table 1 Key interactions with FDA

Type of meeting	Date	Description
Type C meeting	15-Jul-2014	Type C meeting to discuss CMC starting materials
Type B Pre-IND meeting	12-Dec-2014	Type B Pre-IND/Pre-Phase II meeting on clinical development program and overall study design of Study A2201
Type C meeting	02-Feb-2017	Type C meeting to discuss clinical pharmacology and CMC topics related to primary stability batches to support the NDA submission
Type B-EOP2 meeting	01-Mar-2017	Type B EOP2 meeting to discuss Study A2201 for NDA submission
Type C meeting	20-Sep-2018	Type C meeting to discuss overall NDA submission strategy, table of contents, and CMC topics related to 150mg strength change in film-coat color
Type C meeting	30-Jan-2019	Type C meeting to discuss adding a new cohort in first-line setting to Study A2201
Orphan drug designation granted	15-Mar-2019	Orphan drug designation granted for treatment of NSCLC with MET genomic tumor aberrations
Breakthrough therapy designation granted in 2/3L	18-Apr-2019	Breakthrough therapy designation granted for the treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation with disease progression on or after platinum-based chemotherapy
Type B Pre-NDA meeting	22-Jul-2019	Type B Pre-NDA meeting to share top-line results of Study A2201 and discuss proposed NDA submission strategy for the proposed indication
Breakthrough therapy designation granted in 1L	30-Jul-2019	Breakthrough therapy designation granted for the first-line treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation
Rolling review granted	19-Sep-2019	Rolling review proposal to the FDA was granted

1L = first-line treatment; 2/3L = Second-line/ Third-line treatment; CMC = Chemistry Manufacturing & Control; EOP2 = end-of-phase II

The FDA's Assessment:

FDA agrees with Novartis' summary of the pre-submission regulatory activity. During the July 22, 2019 Type B pre-NDA meeting, FDA stated the following:

"The available efficacy and safety data from clinical trials of capmatinib appears adequate to support the filing of a marketing application for capmatinib for the treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation. A decision regarding the adequacy of the data to support accelerated or regular approval and the indicated population will be determined during review of the NDA. The duration of follow-up for responding patients and

the limited number of patients who received capmatinib in the first-line setting may be inadequate to provide substantial evidence of effectiveness to support an approval in this population."

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review division (DO2) and OSI selected four investigator sites, as listed in Section I, for clinical inspections, with a primary focus on subjects in Cohorts 4 and 5b of the study CINC280A2201. Four clinical investigators, Dr. Rebecca Heist (Site 2508), Dr. Maja de Jonge (Site 1803), Dr. Egbert Smit (Site 1802), and Dr. Johan Vansteenkiste (Site 4100), were selected for clinical inspections.

Relative to other investigator sites, these four sites had large numbers of subjects in the two cohorts and/or significant objective responders that are pertinent to assessments of this NDA. Dr. Heist's site (Site 2508) had the highest enrollment among the sites in the United States (U.S.). The reason for selection of the three foreign sites was that 90% of study subjects were recruited from regions outside the U.S. None of the four investigators had a history of FDA inspections prior to this application.

The inspections of Drs. Heist, de Jonge, and Smit were performed, and the results showed that the Applicant's submitted clinical data were verifiable with source records at these three investigator sites, with no evidence of underreporting of adverse events or insufficient protection of study subjects.

The scheduled inspection of Dr. Vansteenkiste in Belgium was cancelled because of the COVID-19 pandemic. OSI discussed with the clinical review team about possible rescheduling the inspection when the COVID-19 pandemic situation improves and/or when the related travel restrictions are lifted. With the feedback obtained from the above three site inspections, the review team informed OSI to withhold this site inspection in the current NDA review cycle. If applicable, this site inspection may be revisited and/or considered in the future when additional data are submitted to the Agency.

Based on the results of the three completed inspections, the clinical data generated from these three investigator sites appear to be reliable and adequate in support of this NDA.

4.2. Product Quality

The CMC review team identified three impurities in the capmatinib drug substance for qualification: (b) (4) (also a minor metabolite in humans and a major metabolite in rats), and (b) (4) plus (b) (4) (b) (4) The proposed shelf-life specifications for

these impurities are no more than (NMT) (b) (4)% and (b) (4)%, respectively. The proposed specifications at levels above the ICH Q3A/B thresholds are justified by the available nonclinical data. See Table 2 for the data supporting the justification.

Table 2: Impurity specification justification

Impurity	Proposed specification (shelf-life)	Daily delivered dose of impurity at capmatinib clinical dose of 400 mg twice daily	Levels in toxicology batch (Rat Study 1570059)	Delivered dose of impurity at STD10 (Rat Study 1570059)	Metabolite?	Specification justified by nonclinical data?
(b) (4)	≤ (b) (4)%	(b) (4) mg/m^2	(b) (4)%	(b) (4) mg/m^2	Yes (b) (4)% in rat and human in vivo)	Yes
	≤ (b) (4)%	(b) (4) mg/m^2	(b) (4)%	(b) (4) mg/m^2	No	Yes

4.3. Clinical Microbiology

Not applicable for this application.

4.4. Devices and Companion Diagnostic Issues

Contemporaneously with review of this NDA, the Center for Devices and Radiological Health (CDRH) reviewed a supplemental premarket application (sPMA) for FoundationOne®CDx that was submitted by Foundation Medicine Inc. on October 16, 2019.

Please refer to the review by Dr. Abdelrahmman Abukhdeir for additional information on the companion diagnostic device.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Capmatinib (INC280) is an orally bioavailable ATP competitive kinase inhibitor that targets the mesenchymal-epithelial transition factor (MET) receptor tyrosine kinase, including the variant produced by an exon 14 skipping mutation in MET. The established pharmacological class is kinase inhibitor. MET alterations, including overexpression, gene amplification, and the exon 14 skipping mutation, drive a subset of non-small cell lung cancers. Deletion of exon 14 removes the binding site of a negative regulatory protein (c-Cbl) that leads to the proteasomal degradation of the receptor. Therefore, with less negative regulation, MET behaves as an oncoprotein, promoting cell survival, proliferation, metastasis, and tumor angiogenesis (Van Der Steen et al., 2016).

In biochemical kinase inhibition screening assays, capmatinib inhibited wild type MET and some MET kinase domain mutations at subnanomolar concentrations; these assays did not identify other targets at clinically relevant concentrations based on IC_{50} data (≤ approximately 0.464 nM based on a Cmax of 4780 ng/mL and 96% protein binding in human plasma). Two active metabolites (M8 and M18) were less potent than capmatinib and represented a minor percentage of exposure compared to the parent drug; the only metabolite present in humans at significant levels was not pharmacologically active in vitro and was present at significant levels in animals as well.

In cellular assays, clinically achievable concentrations of capmatinib inhibited the phosphorylation of MET (due to either certain mutations/amplifications of the receptor or triggered by binding of hepatocyte growth factor) as well as MET-mediated phosphorylation of downstream signaling proteins. Capmatinib also inhibited the proliferation and survival of MET-dependent cancer cells, including cancer cell growth driven by a MET exon 14-associated skipping mutation. Capmatinib demonstrated anti-tumor activity against patient-derived human lung cancer xenografts with either MET exon 14-associated skipping mutations or MET amplifications implanted into nude mice. These studies support the proposed mechanism of action of capmatinib and its activity in the proposed patient population.

In stand-alone safety pharmacology studies, a single dose of 120 mg/kg capmatinib had no notable effects on a CNS or respiratory assessments in male Wistar rats. In a cardiovascular safety study in Cynomolgus monkeys, administration of capmatinib (up to 150 mg/kg) produced no remarkable effects on electrocardiograms or circulatory function (heart rate, systolic and diastolic blood pressure). These findings were consistent with the low potential for QT

prolongation predicted by an in vitro hERG assay (IC_{50} >18.7 µM) as well as the lack of cardiac findings in the 13-week monkey toxicology study and correlated with a lack of significant clinical cardiac electrophysiologic effects.

The Applicant evaluated the toxicity profile of capmatinib in GLP-compliant studies in Sprague-Dawley rats and Cynomolgus monkeys with durations of treatment of up to 13 weeks. Findings in one or both species consistent with clinical experience included decreased albumin and effects on the pancreas (increased amylase and lipase; pancreatic acinar cell apoptosis and vacuolation), liver (elevated ALT, AST, and bilirubin), and kidney (increased blood creatinine).

In rats, capmatinib administration resulted in vacuolation of white matter of the brain in both 4- and 13-week studies at doses ≥2.2 times the human exposure (AUC) at the 400 mg twice daily clinical dose. In some cases, the brain lesions were associated with early death and/or convulsions or tremors. In the 13-week study the minimal increases in vacuolation of the white matter of the brain occurred in all dose groups, including the control; however this finding was present at a slightly increased prevalence in the high-dose males compared with the control, and with increased severity in one male (mild, rather than minimal, in a 60 mg/kg animal at primary necropsy. In addition, vacuolation of the caudate/putamen and vacuolation of the thalamus occurred only at ≥60 mg/kg, including in three high-dose (90 mg/kg) males that died early. The co-occurrence in two high dose males of white matter lesions, convulsions close to the time of death, and early death suggest the relationship of the events. Concentrations of capmatinib in the brain tissue of rats was approximately 9% of the corresponding concentrations in plasma. These findings were not present or present less frequently in recovery animals, suggesting at least some reversibility. It is unknown whether white matter vacuolation occurs in patients treated with capmatinib and events such as seizure and tremor which might be predicted based on these types of lesions were infrequent; however, given the frequency of these findings in rats and the potential for clinical effects at exposures near the expected clinical exposure, FDA included these findings in Section 13.2 of the label.

Carcinogenicity studies were not conducted for capmatinib or necessary for a drug intended for the treatment of patients with advanced cancer. Capmatinib was not mutagenic in an in vitro bacterial reverse mutation assay and did not cause chromosomal aberrations in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Capmatinib was not clastogenic in an in vivo bone marrow micronucleus test in rats. In in vitro and in vivo assays, capmatinib demonstrated some potential for photosensitization; however, the no-observed-adverse-effect level for in vivo photosensitization was 30 mg/kg/day (Cmax of 14000 ng/mL), about 2.9 times the human Cmax at the 400 mg twice daily dose.

Novartis did not conduct fertility studies with capmatinib; consistent with ICH S9, these studies were not warranted for the development of a drug intended for the treatment of patients with

advanced cancer. Novartis did include a histopathological assessment of reproductive organs in all general toxicology studies and there were no clear effects on reproductive organs at doses resulting in exposures of up to approximately 3.6 times the human exposure (AUC) at the 400 mg twice daily clinical dose. To address the potential reproductive effects of capmatinib, Novartis conducted embryo-fetal development studies in rats and rabbits. In rats, there was no evidence of embryo-fetal loss at doses up to 30 mg/kg/day (approximately 1.4 times the human exposure based on AUC at the 400 mg twice daily clinical dose); however, there were fetal effects including reduced fetal weights, irregular/incomplete ossification, and increased incidences of fetal malformations (e.g., abnormal flexure/inward malrotation of hindpaws/forepaws, thinness of forelimbs, lack of/reduced flexion at the humerus/ulna joints, and narrowed or small tongue) at doses of ≥ 10 mg/kg/day (approximately 0.56 times the human exposure [AUC] at the 400 mg twice daily clinical dose). In rabbits, no maternal effects were detected at doses up to 60 mg/kg/day (approximately 1.5 times the human exposure based on AUC at the 400 mg twice daily clinical dose). Fetal effects included small lung lobe at ≥ 5 mg/kg/day (approximately 0.016 times the human exposure based on AUC at the 400 mg twice daily clinical dose), and reduced fetal weights, irregular/incomplete ossification and increased incidences of fetal malformations (e.g., abnormal flexure/malrotation of hindpaws/forepaws, thinness of forelimbs/hindlimbs, lack/reduced flexion at the humerus/ulna joints, small lung lobes, narrowed or small tongue) at the dose of 60 mg/kg/day. The teratogenic findings in animals and role of the mesenchymal-to-epithelial transition in embryonic development (Kim DH et al., 2017) warrant a warning in the label for embryo-fetal risk. In addition, consistent with current recommendations for non-genotoxic compounds with embryo-fetal risk, the label also includes recommendations for the use of effective contraception and avoidance of breastfeeding during treatment and for 1 week following the final dose.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of capmatinib for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for capmatinib.

The FDA's Assessment:
FDA agrees.

5.3. Pharmacology

The FDA's Assessment:
The review of the primary pharmacology included below was conducted by FDA and serves as the FDA assessment of this data.

Primary pharmacology

A. In Vitro Studies

Novartis screened capmatinib for activity against various targets (Studies T07-07-08, RD-2017-00516, and RD-2018-0093). In Study T07-07-08, investigators tested whether 2 µM capmatinib inhibited a panel of 57 human kinases. MET was the only kinase for which capmatinib met the pre-defined cut-off of ≥30% inhibition for a positive result. In subsequent Study RD-2017-00516, investigators performed a competition binding assay that quantitatively measures the ability of a compound to compete with an immobilized, active-site directed ligand. The predefined cut-off for a positive result was ≥65% reduction in binding to the capture matrix compared to a vehicle control. Investigators tested 10 µM capmatinib against a panel of 442 kinases and mutant kinase variants. Hits included wild-type MET, MET mutants M1250T and Y1235D, and 6 other kinases. Investigators determined the Kd values for the 9 hits (Study RD-2018-0093). The average Kd values for the 3 MET hits was 0.5 nM, and the next lowest Kd was 500 nM, yielding a selectivity factor of capmatinib for MET of approximately 1000 or greater.

Table 3: Kinase selectivity of capmatinib against a panel of 442 human kinases and mutant kinase variants

Kinase	% of control at 10 µM	Kd (nM)
ABL1(H396P)-nonphosphorylated	13	3200
AXL	12	1100
CDK11	23	5700
IRAK1	1.6	500
MET	3.6	0.31
MET(M1250T)	1.2	0.69
MET(Y1235D)	2.4	0.53
PIP5K2C	24	>10000
YSK4	17	2100

Capmatinib was screened at 10 µM, and results of the primary screen are reported as % of control, where lower numbers indicate stronger hits. All other tested kinases scored at ≥ 35% (not considered hits) and are not listed here. Binding constants (Kd) were determined for all hits from the primary screen.

(Excerpted from the Applicant's submission: Module 2.6.2)

Investigators treated two cell lines with constitutively activated MET (SNU-5 and S114) and six lines that required HGF stimulation, with a range of concentrations of capmatinib and used a cellular phospho-MET ELISA assay to determine the IC_{50} for inhibition of MET phosphorylation in each line (Liu et al., 2011, which is an Applicant publication). Capmatinib inhibited each line, with IC_{50} values ranging from 0.3 and 1.4 nM (Table 4). The IC_{50} value for the NCI-H596 lung

cancer line, driven by a MET exon 14 skipping mutation, was 0.4 nM.

Table 4: Capmatinib activity in various cellular assays

Table 2-3 Capmatinib activity in various cellular assays

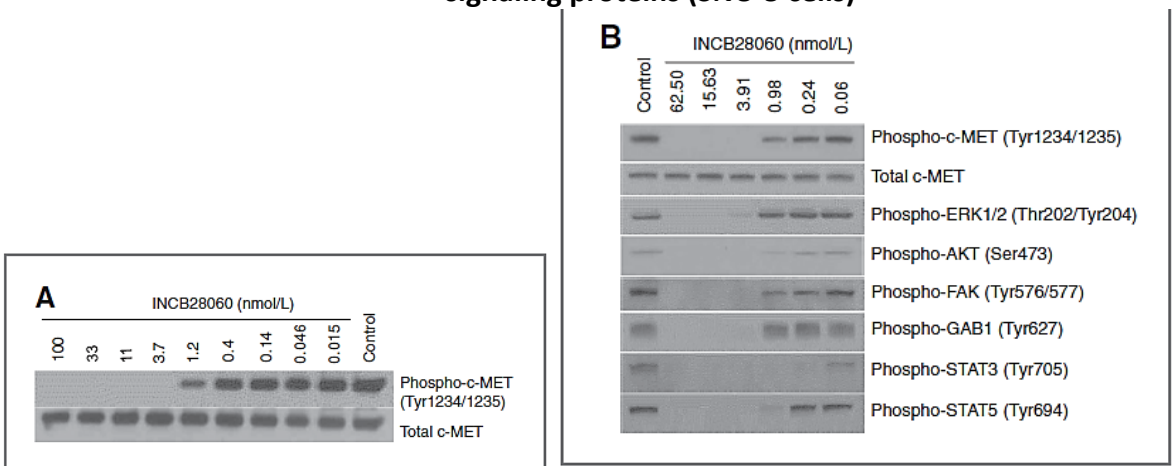
Assay	Enzyme source/Cell line (tissue type)	IC_{50} (nM) [a]	N
Cellular phospho-MET			
Constitutive	SNU-5 (gastric)	1.1 ± 0.4	28
	S114 (transfected mouse fibroblasts)[b]	0.9	2
HGF stimulated	A549 (lung)	0.7	2
	U-87 MG (glioblastoma)	1	2
	786-O (kidney)	0.6	2
	NCI-H441 (lung)	0.7	2
	NCI-H596 (lung)[c]	0.4	2
	NCI-H1437 (lung)[c]	0.3	2
Cell proliferation	SNU-5 (gastric)	1.2 ± 0.4	28
	S114 (transfected mouse fibroblasts)	12.4	2
	SNU-1 (gastric)	>10'000	2
	HEK293 (kidney)	>20'000	2
Soft-agar colony formation	NCI-H441 (lung)	~ 0.5	2
	U-87 MG (glioblastoma)	~ 2	2
Migration/wound healing	NCI-H441 (lung)	~ 2	2
Apoptosis/DNA fragmentation	SNU-5 (gastric)	detectable at 1 nM	3

[a] Values are mean ± standard deviation for n > 2, and simple mean or estimated values for n = 2.
[b] Genetically engineered mouse fibroblast cell line that overexpresses both MET and HGF (Rong et al 1992).
[c] H596 and H1437 bear a MET exon 14 skipping mutation or MET-R988C mutation, respectively. Both mutations are located in the juxtamembrane domain of the receptor.
Source: [nonclinical-summary-IND-103729] (Liu et al 2011)

(Excerpted from the Applicant's submission: nonclinical-summary-IND-(b) (4) and Liu et al, 2011)

SNU-5 human gastric cancer cells carry a MET amplification, resulting in constitutively activated MET. Investigators treated SNU-5 cells with capmatinib over a range of concentrations for 2 hours and then lysed cells and measured the phosphorylation of both MET and several downstream signaling proteins including ERK1/2, AKT, FAK, GAB1, STAT3/5 via Western blot (Liu et al., 2011). At a concentration of 3.7 nM, capmatinib inhibited MET phosphorylation and at 3.9 nM it also inhibited the phosphorylation of downstream targets ERK, FAK, and GAB1 (Figure 1); lower capmatinib concentrations were sufficient for inhibition of AKT, STAT3, and STAT5.

Figure 1: Capmatinib inhibits MET phosphorylation and phosphorylation of downstream signaling proteins (SNU-5 cells)



(Excerpted from the Applicant's submission: Liu et al, 2011)

The SNU-5 human gastric carcinoma cell line depends on MET and is sensitive to capmatinib inhibition, while the SNU-1 human gastric carcinoma cell line negative control does not express MET and is insensitive to capmatinib (Liu et al, 2011). In SNU-5 but not SNU-1 cells, capmatinib inhibited cell viability (Figure 2-A), and caused a dose-dependent increase in DNA fragmentation (Figure 2-C) and PARP cleavage (Figure 2-D), reflecting apoptosis.

Figure 2: Capmatinib inhibits MET-dependent cell proliferation and survival

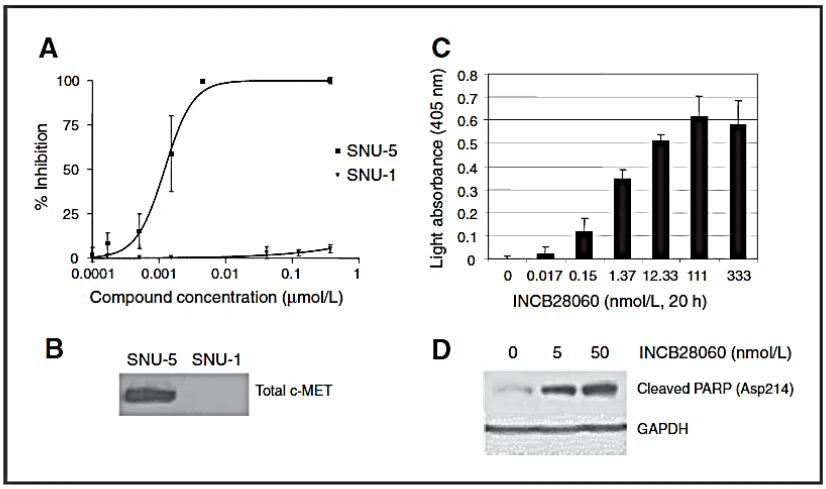


Figure 2. INCB28060 inhibits c-MET–dependent cell proliferation and survival. A, the indicated cell lines were cultured for 3 days in appropriate media containing 2% FBS in the presence of various concentrations of INCB28060, and cell viability was measured by MTS assay. The composite curve of percentage inhibition of cell viability by INCB28060 was plotted using average values of multiple experiments ± SD. B, Western blot detection of c-MET protein in SNU-5 and SNU-1 cells. C, SNU-5 cells were grown in low-serum medium overnight and treated with INCB28060 at the indicated concentrations for 20 hours. DNA fragmentation analysis was carried out with the treated cells, and representative data showing levels of DNA fragmentation from 3 independent experiments are presented. D, SNU-5 cells receiving similar treatments to (C) were lysed for protein extraction and then subjected to Western blot detection of cleaved PARP. Result of a representative experiment is presented. GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

(Excerpted from Liu et al, 2011)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Activity of metabolites

Investigators assessed three metabolites of capmatinib, M8, M16, and M18, in biochemical and cellular assays (Study RD-2014-00427). M16 lacked activity. M8 and M18 were less potent than capmatinib and their systemic exposures were approximately 13% and <7% of capmatinib exposure, respectively. Investigators also tested the 3 metabolites against a panel of 29 kinases and no target besides MET was affected.

Table 5: Relative biochemical and cellular activity of metabolites M8, M16, and M18 compared to capmatinib

Compound	Kinase assay, IC_{50} (nM)	Kinase assay, factor	Cellular assay, IC_{50} (nM)	Cellular assay, factor
INC280	1.7	1	3.5	1
M8 (CMN290)	36.5	22 (9.7)	181	52 (22.9)
M16 (CMN288)	>10000	NA	>10000	NA
M18 (CNJ294)	13	8	8.6	2.5

Relative activities (factors) were calculated by dividing the average IC_{50} values of the respective metabolites by the average IC_{50} value of the parent compound INC280. For M16, no such factor could be calculated since the metabolite is inactive (NA = not applicable). For M8, factors in brackets were calculated under the hypothetical extreme assumption that only the enantiomer that represented 44% of the tested batch was active, and that this enantiomer constitutes 100% in patients.

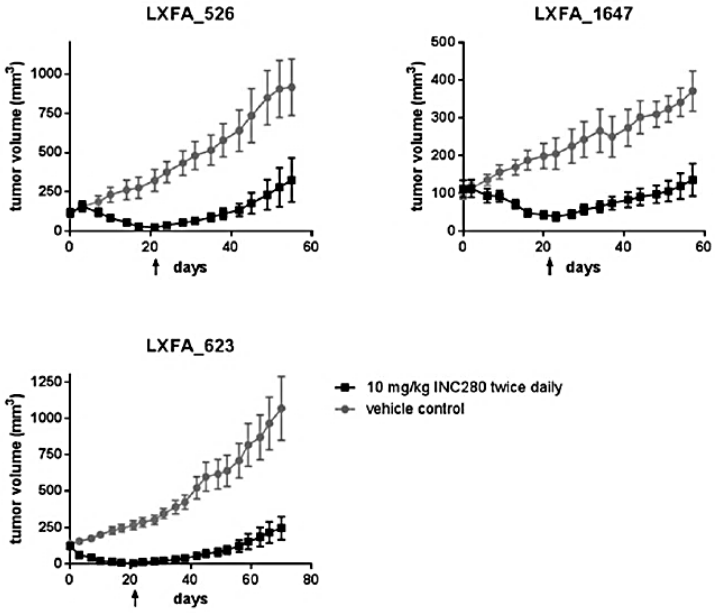
(Applicant Table excerpted from Study RD-2014-00427)

B. <u>In Vivo Studies</u>

Non-small cell lung cancer xenograft studies

Investigators measured MET gene copy numbers in a panel of 39 patient-derived xenografts and selected the three with the highest expression, up to a copy number of 31.3: LXFA_526, LXFA_623, and LXFA_1647 (NSCLC adenocarcinomas) (Study RD-2013-00315). Investigators implanted the xenografts into immunocompromised female NMRI nu/nu mice. When tumor reached a volume range of 50 to 250 mm^3, animals were randomized and stratified into groups by tumor volume. Animals received capmatinib twice daily (20 mg/kg/day) or vehicle control via oral gavage for 18 days. Due to body weight loss, investigators reduced the capmatinib dose to 10 mg/kg once daily for Days 14 through 18. Mice were observed for up to seven weeks after the end of treatment. Capmatinib resulted in transient partial regression of tumors (-65.5%, -79.3% and -96.2% for LXFAs 1647, 526 and 623, respectively.)

Figure 3: Anti-tumor activity of capmatinib against three NSCLC lung cancer PDX models

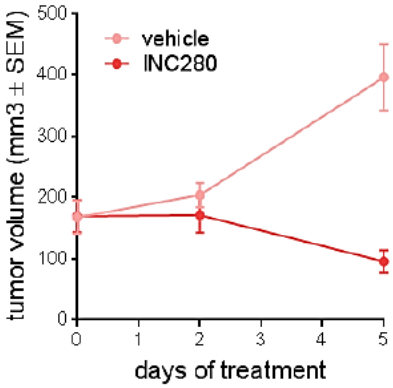


(Applicant figure excerpted from Study RD-2013-00315)

MET exon 14 skipping mutation xenograft study

Investigators evaluated the in vivo anti-tumor activity of capmatinib against LU5381 tumor cells, a patient-derived NSCLC line driven by the MET exon 14 skipping mutation and lacking a high level of MET amplification (copy number: 5.17) (Study RD-2018-00057). LU5381 cells were mixed with an extracellular matrix hydrogel and implanted subcutaneously in the rear flanks of 10 immunodeficient female NOD-SCID mice. When the average tumor volume reached approximately 170 mm^3, mice were randomized to receive a single dose level of capmatinib (20 mg/kg/day) or vehicle control, via twice daily oral gavage for 6 days. Tumor volumes were measured on Days 3 and 6. On Day 6, prior to sacrifice of all animals, capmatinib treatment resulted in significant anti-tumor activity compared to the control and a slight decrease in body weight (approximately 4% or less).

Figure 4: Anti-tumor activity of capmatinib against a MET exon 14 skipping mutation-driven NSCLC lung cancer PDX model



(Applicant figure excerpted from Study RD-2018-00057)

S114 is an NIH 3T3 line stably expressing human HGF and MET (Liu et al., 2011). Investigators studied the anti-tumor activity of capmatinib in the S114 allograft model in Balb/c nu/nu mice. Twice daily oral capmatinib treatment resulted in near-complete inhibition of tumor growth through Day 13 at doses ≥ 10 mg/kg (Figure 5-C). Investigators extracted tumors and measured phospho-MET levels (via a Human Phospho-HGFR/MET kit) 30 minutes after treatment with capmatinib at doses ranging from 0.03 to 10 mg/kg (Figure 5-A), and at 1, 4, 7, 10, and 24 hours after treatment with 3 mg/kg (Figure 5-B). Doses ≥0.3 mg/kg reduced MET phosphorylation by approximately 90%. At the 3 mg/kg dose level, capmatinib reduced MET phosphorylation by at least 80% during the first 10 hours post dosing. Anti-tumor activity appears to correlate with reduction in MET phosphorylation.

Figure 5: Capmatinib inhibits tumor growth and MET phosphorylation in the S114 model

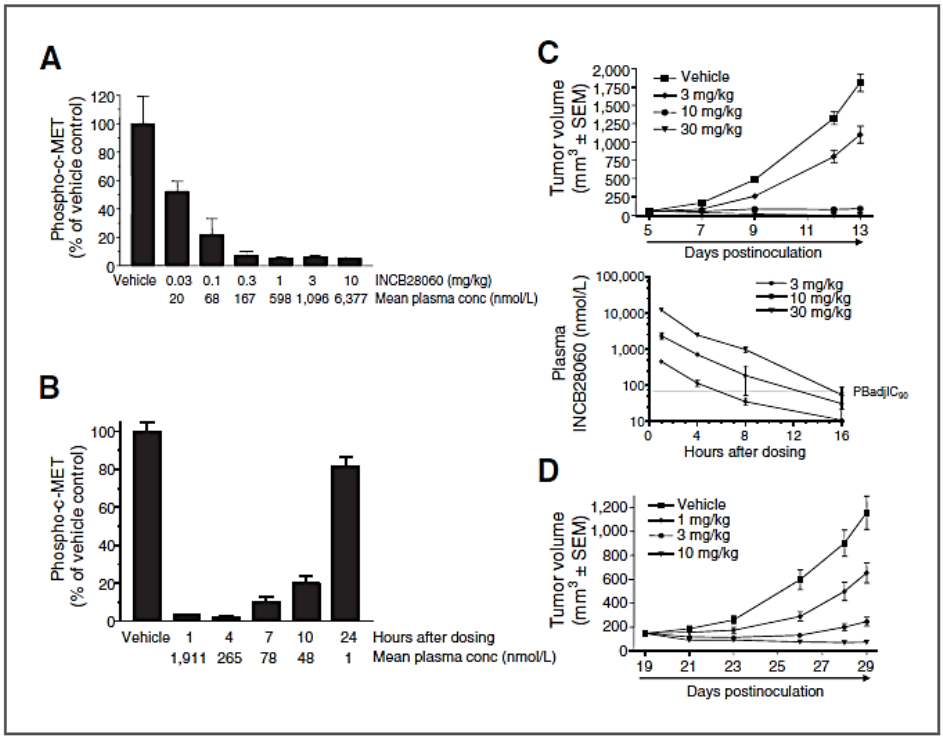


Figure 4. INCB28060 inhibits c-MET phosphorylation and tumor growth in c-MET–dependent mouse tumor models. Equal amounts of protein extracts of tumor tissues from S114 tumor–bearing mice were analyzed for phospho-c-MET levels. Representative data are presented for dose-dependent inhibition of phospho-c-MET by INCB28060 at 30 minutes postdose (A) and for inhibition of phospho-c-MET over time by a single dose of 3 mg/kg INCB28060 (B). In (A) and (B), a group of 8 mice was used to generate each data value, and mean ± SEM are shown. For INCB28060 exposure, mean plasma concentrations are presented. Representative data of dose-dependent tumor growth inhibition are shown in the S114 model (C) and in the U-87MG model (D). Mean tumor volumes ± SEM are shown for the S114 model ($n = 8$ mice per group) and U-87MG model ($n = 10$ mice per group). For INCB28060 exposure, mean plasma concentrations ± SEM for the first 16 hours of day 1 treatment are shown for the S114 model ($n = 8$ mice per group) in (C). PBadjIC$_{90}$, protein binding–adjusted IC$_{90}$. The arrow-headed lines below the graphs in (C) and (D) indicate the days when the animals were treated with the compound.

(Excerpted from Liu et al., 2011)

Secondary Pharmacology

Data [Summarized by the Applicant]:

In the in vitro screening assay, capmatinib was assessed for its off-target activity on 154 unique targets (103 GPCRs, 6 transporters, 27 ion channels, 6 nuclear receptors, 1 cytokine receptor, 1 sigma receptor and 10 enzymes) at concentrations up to 30 µM.

Activities below 10 µM were found in the rat VMAT2 monoamine transporter uptake assay (IC50 = 2.0 µM), the angiotensin receptor AT1 binding assay (IC50 = 4.4 µM), the phosphodiesterases PDE3 (IC50 = 4.7 µM,) and PDE4 (IC50 = 5.1 µM) and the acetylcholinesterase assay (IC50 = 5.7 µM).

The Applicant's Position:

Based on the estimated human therapeutic plasma free drug Cmax of 0.464 µM, and the extrapolated human brain free-drug Cmax of 0.0464 µM (assuming 10% brain penetration based on rat study 1170512), capmatinib at therapeutic doses is not expected to have relevant effects on CNS related off-targets (VMAT2, PDE4 and acetylcholine esterase), and no significant effects due to non-CNS off-target binding (AT1, PDE3, PDE4 or acetylcholinesterase).

The FDA's Assessment:
FDA agrees that the potential off-target activity of capmatinib appears low based on this screen.

Safety Pharmacology

Data [Summarized by the Applicant]:

hERG Assay:
In this GLP manual patch clamp hERG assay, capmatinib dissolved in 0.3% DMSO was tested for effects on hERG current using voltage-clamped human embryonic kidney cells (HEK293) at concentrations of 3, 10 and 30 µM. Capmatinib inhibited hERG current by 13.7%, 36.7% and 60.6% at 3, 10 and 30 µM, respectively with estimated IC50=18.7 µM.

CNS and respiratory function test:
In the GLP CNS and respiratory function test, capmatinib at doses of 0 and 120 mg/kg were administered to Wistar rats by oral gavage, and tested for CNS effects by functional observation battery (FOB) assessment. Following a 6-day washout, the control animals of the FOB assessment phase were assigned to the respiratory evaluation phase, where each male rat received a dose of vehicle and 120 mg/kg of capmatinib following a crossover paradigm design with 7 days between the doses.
No test article related deaths or clinical signs were observed following a single oral administration of capmatinib at 120 mg/kg; no test article-related effects were observed on any of the quantitative and qualitative FOB parameters up to 24 hours post dose. No test article-related effects were noted on the respiratory system of male rats following a single oral administration of capmatinib at a dose of 120 mg/kg.
In conclusion, the oral administration of capmatinib to male Wistar rats as a single dose of 120 mg/kg produced no test article-related effects on the central nervous system or respiratory system.

Cardiovascular safety assessment:
In the GLP cardiovascular safety study, hemodynamic and electrocardiographic parameters were evaluated in the male cynomolgus monkey via telemetry following a single oral

administration. Capmatinib was administered to each of the male monkeys at doses of 0, 30, 75 and 150 mg/kg, with 7 days between each dose, to complete a 4 x 4 crossover paradigm.
All animals had the following parameters collected: clinical signs and mortality, detailed examinations, systemic blood pressures (mean arterial pressure, systolic blood pressure and diastolic blood pressure, pulse pressure), heart rate, electrocardiographic duration/intervals (PR, RR, QRS, QT, QTc and QA intervals), qualitative evaluation of the electrocardiographic waveforms twice prior to each dose (at least 30 minutes apart) and at approximately (±15 minutes) 30 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 and 24 hours post dose for each dose.
No deaths or test article-related clinical signs were noted following a single oral exposure to capmatinib at dose levels of 30, 75 and 150 mg/kg.
No test article-related effects were noted on systemic blood pressures (systolic, diastolic, mean arterial and pulse pressure), heart rate, QT, QTc, PR, QRS or QA intervals following the administration of capmatinib at doses of 30, 75 and 150 mg/kg.
No abnormalities in rhythm or waveform morphology were found at any dose level based on comparison of predose and postdose electrocardiographic recordings.
In conclusion, a single oral administration of capmatinib did not result in any test article-related hemodynamic or electrocardiographic changes at dose levels of 30, 75 and 150 mg/kg. There were no abnormal electrocardiographic findings detected from the administration of capmatinib.

The Applicant's Position:
Safety pharmacology studies with capmatinib indicated no significant effects on cardiac, CNS or respiratory functions. hERG IC50 is at 40 times the expected free drug Cmax (0.464 µM) at maximal therapeutic dose of 400 mg bid in humans.

The FDA's Assessment:
FDA generally agrees with the Applicant's conclusions; however, despite the lack of significant acute CNS effects in rats in single-dose safety pharmacology study 1070421, there may be capmatinib-related CNS toxicity based on findings in repeat-dose studies in which rats experienced convulsions or tremors (T08-04-11 and T10-02-02) after a minimum of 4 daily doses (onset of event: between Days 4 and 24). The results of the hERG assay and in vivo monkey telemetry study are consistent with the lack of a clinically meaningful effect of capmatinib on human cardiac electrophysiology.

5.4. ADME/PK

Data [Summarized by the Applicant]:

Absorption
Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride: DMPK R1100027-

01; *Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280: DMPK R1300820*
Absorption of capmatinib was estimated as 51.1% in rat and as complete in monkey. Based on iv and po administration of capmatinib in male rats and monkeys, oral bioavailability showed a significant species and inter-study variability (range between 24% and complete bioavailability). No major first-pass metabolism could be concluded for rats and monkeys.
A substantial gender-related difference in toxicokinetics was observed in rats but no or minimal gender differences in exposure were observed for monkey.

Following single iv dosing, blood clearance was moderate in male rats (0.42-1.79 L/(h·kg)) as well as monkeys (0.11-0.32 L/(h·kg), compared to the hepatic blood flow. In male rats capmatinib was cleared from plasma with a terminal elimination half-life of 1.4 to 3.6 hours. In the monkey ADME study, the decay in capmatinib plasma concentrations appeared to be bi-exponential. The initial T1/2, α of 0.66 hours was short. However, the terminal phase half-life (T1/2, β) of 88 hours was long contributing to only 27% of the AUCinf based on two compartmental analyses.

Distribution
Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [14C]INC280 dihydrochloride: DMPK R1100027-01, Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administration of 40 mg/kg/day [14C]INC280: DMPK R1600074-01
In the rat, radiolabeled capmatinib and/or its metabolites distributed rapidly into tissues and passed the blood-brain barrier with brain to plasma ratio of approximately 9%. In pigmented rats, the highest exposure of total radiolabeled components based on Cmax and AUClast was observed in melanin-containing tissues. Melanin containing structures such as eye (choroid) and eye (ciliary body) appeared to show specific uptake and prolonged retention of drug related material as concentrations of total radiolabeled components. In albino rats, the tissue distribution pattern was qualitatively similar after single and multiple dosing. Following multiple oral doses to rats the highest exposure of total radiolabeled components, were observed in preputial gland, liver, stomach (glandular and non-glandular), intestinal wall (small intestine), kidney (CM junction and cortex), and blood vessel wall. The highest accumulation was observed in eye (lens) and adrenal (medulla).

FDA Additional Comment on Distribution (Protein Binding):
The In vitro protein binding of INCB028060 in human, cynomolgus monkey, dog, rat and mouse serum and plasma and ex vivo protein binding in cynomolgus monkey and rat plasma: INCYTE-DMB-08.122.1
The percent protein binding of capmatinib (average of serum and plasma values across doses) was similar for humans and rats (94.6% and 94.5%, respectively) but was slightly higher in

monkeys (97.2%). Percent protein binding was lower in the dog (81.8%), which was not chosen for a pivotal toxicology study.

Metabolism

Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [14C]INC280 dihydrochloride: DMPK R1100027-01, Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [14C]INC280: DMPK R1300820

In vivo metabolism of capmatinib was investigated in rat, monkey and human. The biotransformation of capmatinib occurred essentially by phase I metabolic reactions including C-hydroxylation, lactam formation, hydrogenation, N-oxidation, N-dealkylation, carboxylic acid formation and combinations thereof. Phase II reactions involved glucuronidation of oxygenated metabolites. The lactam metabolite M16 was formed in rat, monkey and human and was the only major circulating metabolite in human which amounted to greater than 10% of the total drug-related exposure. After single- or multiple-dose administration to patients, the plasma exposure of the metabolite M16 was substantial, but with lower metabolite-to-parent AUC ratios of 0.398 and 0.269, respectively, when compared to ratios in rat (0.99) and monkey (0.32-0.61). Adequate systemic exposure of M16 was obtained in the toxicology species rat and monkey. The contribution of metabolite M16 and other minor human metabolites M8 and M18 to the total pharmacological activity in human is negligible (<4%).

Excretion

Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [14C]INC280 dihydrochloride: DMPK R1100027-01, Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [14C]INC280: DMPK R1300820

In rat and monkey, the major route of excretion was fecal. Following oral dosing of radiolabeled capmatinib, 72 to 86% of the administered radioactivity was found in feces and 8 to 10% in urine.

Capmatinib was eliminated in rat and monkey mainly by metabolism, and subsequent biliary/fecal excretion. After iv or po administration, unchanged capmatinib was either not detected in urine or was detected only in trace amounts. In feces of rat and monkey, capmatinib accounted for between 5% and 12% of the oral or iv dose.

In bile duct-cannulated male rats dosed iv with 14C-capmatinib, the majority of the administered radioactivity was collected in the bile and only a minor part in the urine or feces. In bile, capmatinib was not detected, demonstrating that biliary secretion of metabolites is indeed the major elimination route in rat. Low intestinal secretion of capmatinib (2.3% of the

dose) was found in bile duct-cannulated rats. Recovery of radioactivity in mass balance studies was close to complete or complete (85%-100%) in rat and monkey.

TK data from general toxicology studies

The oral toxicokinetics of capmatinib in rat were determined from seven studies: e.g. 9 days (20, 40, 80, 200 mg/kg/day, [Study T08-02-12]), 4 weeks (20, 60, 120 mg/kg/day in males and 10, 30, 60 mg/kg/day in females, [Study T08-04-11]), 6 weeks (60, 90 mg/kg/day in males, [Study 1370733]) 13 weeks (20, 40, 60, 90 mg/kg/day in males and 10, 20, 30, 45 mg/kg/day in females, [Study T10-02-02]), embryo fetal development in pregnant females at (1, 10, 30 mg/kg, [Study 1170160]), 4 weeks investigative toxicity study (60, 90 mg/kg/day in males, [Study 1170512]), 4 weeks impurity qualification study (20, 60 mg/kg/day in males and 10, 30 mg/kg/day in females, [Study 1570059]).

In monkeys, the toxicokinetics of capmatinib were determined in three repeated dose studies: rising dose study (20, 50, 150, 600 mg/kg/day, [Study T07-11-13]), 4 weeks (30, 75, 150 mg/kg/day, [Study T08-01-08]), 13 weeks (10, 30, 75 mg/kg, [Study 1070417])

In rats after oral doses between 10-200 mg/kg/day, exposure generally increased with increasing dose though not always in a dose proportional manner. After multiple once daily applications, accumulation of capmatinib was low at all dose levels (≤ 2-fold). Gender-dependent toxicokinetics were observed in rats. Male rats exhibited only 30-50% of the exposure of female rats from the same dose group.

In monkeys after oral doses between 10-600 mg/kg/day, exposure increased with increasing doses though not always in a dose proportional manner. In contrast to data obtained from mice and rats, no consistent gender difference in exposure was found. After multiple once daily applications, no accumulation of capmatinib was observed at all doses and in both genders.

FDA Additional Comment on Toxicokinetic Data: Slight accumulation of capmatinib occurred at the 75 mg/kg dose level in monkeys.

Table 6: Toxicokinetic data: Day 28 vs. 87 (13-week study; Monkeys)

	Dose (mg/kg)	AUC (ng*hr/mL)	Day 87 / Day 28
Day 28 (sexes averaged)	10	7915	
	30	30950	
	75	73350	
Day 87 (sexes averaged)	10	7205	0.9
	30	32850	1.1
	75	99150	1.4

TK data from reproductive toxicology studies [Summarized by the Applicant]

Rat and rabbit an oral (gavage) embryo-fetal development study, toxicokinetic analyses [Study 1170160] for rat, [Study 1170159] for rabbit.
In the rat embryofetal development study, the maternal systemic exposure at the doses of 1 (NOAEL), 10 and 30 mg/kg/day was AUC0-24hr = 1810 ng*hr/mL, 22,700 ng*hr/mL and 56,300 ng*hr/mL, respectively.
In the rabbit embryofetal development study, the maternal systemic exposure at the doses of 1 (NOAEL), 5 and 50 mg/kg/day was AUC0-24hr = 48.6 ng*hr/mL, 630 ng*hr/mL and 59,400 ng*hr/mL, respectively.

FDA Comment: The high dose in the rabbit study was 60 (not 50) mg/kg/day.

TK data from Carcinogenicity studies
Not applicable

The Applicant's Position:
Pharmacokinetics and disposition of capmatinib were investigated in the species utilized in toxicity testing. The fate of capmatinib appears to be similar in all toxicity species investigated including human. Hence, animal data were meaningful to assess the human safety. Oral bioavailability was moderate-to-high in rats and monkey. Tmax was consistent and ranged between 0.25 to 7 hours across all species after po dosing. Capmatinib showed low to moderate blood clearance in all species following iv dosing. The terminal plasma elimination half-life and volume of distribution were low-to-medium across all preclinical species compared to human with a short elimination half-life. In rats and mice, a gender difference in toxicokinetics was observed which could be explained by a gender-dependent expression of CYP enzymes and aldehyde oxidase in rats and mice. No gender difference in toxicokinetics was found in monkey and human.

Plasma protein binding was high in all species except for dog. In the rat dosed with radiolabeled capmatinib, extensive distribution of radioactivity was seen with moderately fast elimination from most tissues. In pigmented rats, radioactivity was reversibly distributed into the melanin containing structures such eye choroid. The highest accumulation was observed in eye (lens) and adrenal (medulla). Brain penetration of capmatinib was minor in rat and showed no accumulation after multiple dosing.

Capmatinib underwent extensive metabolism assessment in rat, monkey and human. The biotransformation of capmatinib occurred essentially by phase I metabolic reactions including C-hydroxylation, lactam formation, hydrogenation, N-oxidation, N-dealkylation, carboxylic acid formation and combinations thereof. Phase II reactions involved glucuronidation of oxygenated metabolites. A major component in plasma of rat, monkey and human was unchanged capmatinib. The most prominent plasma metabolite in human was the lactam metabolite M16.

The metabolite was found as a major metabolite in the systemic circulation of rat and monkey. Hence, exposure to the main human plasma metabolite (>10% total drug related exposure) was covered by the toxicology species. M16 had no meaningful contribution to the total pharmacological activity in human.

In all species, excretion of drug-related material was mainly via the fecal route with no or negligible contribution by elimination into urine. Elimination was driven by metabolism without contribution of renal clearance. In rat bile, unchanged capmatinib was not detected. Minor enteric secretion of capmatinib was found in the rat. Overall, the disposition characteristics of capmatinib in human and the toxicological species (rat, monkey) do supports the selection of the species used in pharmacology and toxicity studies, and the extrapolation of efficacy and safety data to humans.

The FDA's Assessment:

FDA confirmed Novartis's representation of the ADME data based on the submitted reports and generally agrees with the presentation of the findings. In addition to inactive metabolite M16, two minor metabolites (M8 and M18) with pharmacologic activity less potent than that of capmatinib, (Study RD-2014-00427) were present in rats and monkeys at levels high enough to cover exposure of metabolites at the clinical dose. Unique human metabolites each represented less than 10% of total exposure and therefore did not require additional toxicological coverage. No additional nonclinical ADME studies are warranted.

5.5. Toxicology

[Summarized by the Applicant] An extensive toxicology safety evaluation program (single dose and repeated dose toxicity, genotoxicity studies, reproductive toxicology, phototoxicity) was conducted to support the chronic oral administration of capmatinib to cancer patients. The program of studies has been designed consistent with the ICH S9 guideline. Nonclinical safety studies summarized in this document were performed either at Incyte Pharmaceuticals, Novartis Pharmaceuticals or outsourced by Incyte or Novartis to a contract research organization. All pivotal toxicity studies were performed in accordance with Good Laboratory Practices (GLP) and accepted guidelines.

5.5.1. General Toxicology

Data [Presented by the Applicant]:

Single dose studies were conducted in mice, rat and monkeys. Repeated dose studies were conducted in mice for 8, 6, 7 days (non-GLP), in rats for 9 days (non-GLP), 28 days (GLP) and 13-weeks (GLP), and in cynomolgus monkeys for 7 days (non-GLP), 28 days (GLP) and 13-weeks (GLP). The results of 13-week GLP toxicity studies in rats and cynomolgus monkeys are

summarized below. Both rat and monkey are considered pharmacologically and metabolically relevant species.

A 3-months oral toxicity and toxicokinetic study in Sprague Dawley rats with a 13-week recovery / Study T10-02-02:

Key Study Findings

- Capmatinib was not tolerated in males at ≥ 60 mg/kg/day and females at ≥ 30 mg/kg/day as evidenced by mortality. Dosing for the high-dose group (90 mg/kg/day males and 45 mg/kg/day females, respectively) was suspended during study weeks 4 and 8, respectively, due to mortality.
- Treatment related tremors and convulsions were noted in small number of animals at the high dose (the 90 mg/kg/day males and 45 mg/kg/day females). Histopathology findings included degeneration and vacuolation in the brain of the ≥ 60 mg/kg/day males, pancreatic acinar cell apoptosis in ≥ 60 mg/kg/day males and 45 mg/kg/day females.
- All findings were reversed after 13-week recovery period.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	Males: 20, 40, 60, 90 mg/kg/day; Females: 10, 20, 30, 45 mg/kg/day; Once daily
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% (w/v) methyl cellulose (400 cps) in deionized water
Species/Strain:	Rat / Sprague Dawley
Number/Sex/Group:	15 for main study, 8 for recovery
Age:	7-8 weeks
Satellite groups/ unique design:	N=4/sex in control and N=10/sex for treatment group for toxicokinetics
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	Mortality observed in males at 60 and 90 mg/kg/day, in females at 30 and 45 mg/kg/day. Early termination of males at 90 mg/kg/day and females at 45 mg/kg/day due to mortality.
Clinical Signs	Tremors and/or convulsions males at 90 mg/kg/day and females at 45 mg/kg/day.
Body Weights	Test article-related lower body weight gains were noted in the 90 mg/kg/day group males and the 45 mg/kg/day group females during the dosing period, especially in males.
Ophthalmoscopy	No findings
Hematology	Hematology alterations included a recoverable, non adverse, modest lymphocytosis in males at dosage levels ≥ 40 mg/kg/day and in the 30 mg/kg/day group females. Additionally, the monocyte and large unstained cell counts were higher in the 60 mg/kg/day group males.
Clinical Chemistry	Serum chemistry alterations included lower potassium concentrations in the 60 and 90 mg/kg/day group males and the 20 and 30 mg/kg/day group females. Additionally, a higher amylase concentration was noted in the 60 mg/kg/day group males.
Urinalysis	No findings
Gross Pathology	No findings
Organ Weights	No findings
Histopathology	Microscopic findings included lesions in the brain (white matter vacuolation and/or degeneration in thalamus/caudate/putamen) of the ≥ 60 mg/kg/day group males, and pancreas (acinar cell apoptosis) of the ≥ 60 mg/kg/day group males and 45 mg/kg/day group females.
Other evaluations	FOB and locomotor activity (FOB/MA) data were recorded during study week 3 (all groups) and during the last week of dosing for Groups 1 to 4 (study week 12). A test article-related effect on locomotor activity patterns was noted in the 60 and 90 mg/kg/day group males as evidenced by slightly lower total and ambulatory counts for the overall 60-minute test session at study week 3 and/or 12.
LD: low dose; MD: mid dose; HD: high dose. -: indicates reduction in parameters compared to control.	

FDA Additional Comment: FDA has included the toxicokinetic data from the 13-week rat study as reference.

Table 7: Toxicokinetic data (13-week study; Rats)

Dose level (mg/kg)	Day 56*		Day 90	
	AUC_{0-24} (µM*hr)	Exposure multiple	AUC_{0-24} (µM*hr)	Exposure** multiple
Males				
20	48	0.5	58	0.6
40	96	1.0	118	1.2
60	127	1.3	254	2.6
90	222	2.3	-	-
Females				
10	44	0.4	42	0.4
20	76	0.8	94	1.0
30	175	1.8	155	1.6
45	182	1.9	-	-

*Day 28 for males at 90 mg/kg due to early death/sacrifice; - no data collected due to early death/sacrifice; **AUC_{0-24} at the human clinical dose: 98 µM*hr

The FDA's Assessment:

FDA generally agrees with the Applicant's summary. The major concern for capmatinib toxicity based on the rodent data was the potential for CNS toxicity. At the high dose level in the 4-week studies there were minimal findings of white matter vacuolation in the brain that were more frequent in animals that died or were sacrificed early. In the 13-week rodent study, minimal vacuolation of the white matter of the brain occurred in all dose groups, including the control; however there was increased prevalence in the high-dose males compared with the control, and with increase severity in one male (mild, rather than minimal, in a 60 mg/kg animal at primary necropsy. In addition, vacuolation of the caudate/putamen and vacuolation of the thalamus occurred only in males at doses ≥60 mg/kg. Vacuolation of the caudate/putamen also occurred in three high-dose males that died early. The co-occurrence in two high dose males (#2627 and #2651) of white matter lesions, convulsions close to the time of death, and early death suggest the relationship of the events. While brain vacuolation persisted in recovery animals, the severity was the same in treated animals vs controls and vacuolation in the caudate/putamen or thalamus was not present, suggesting at least partial reversibility.

Table 8: CNS-related histopathology data (13-week study; Rats)

Finding Group (dose mg/kg)		0	20	40	60	90
Primary necropsy, Males, Groups 1-4	**# examined**	**15**	**14**	**15**	**14**	**0**
Brain degeneration, thalamus, minimal					1	--
Brain vacuolation increased, white matter						
-- minimal		5	4	5	2	--
-- mild					1	--
Brain vacuolation, white matter, caudate/putamen, minimal					2	--
Brain vacuolation, white matter, thalamus, mild					1	--
Recovery necropsy, Week 26, Males, Groups 1-4	**# examined**	**8**	**8**	**8**	**7**	**0**
Brain vacuolation increased, white matter, minimal		3	4	1	3	--
Brain inflammation, chronic, meninges, mild					1	--
Necropsies of Males found dead	**# examined**	**0**	**1**	**0**	**2**	**8**
Brain vacuolation increased, white matter, minimal					2	1
Brain vacuolation, white matter, caudate/putamen						
-- minimal						1
-- mild						1
Recovery necropsy, Week 17, Males, Group 5	**# examined**	**0**	**0**	**0**	**0**	**8**
Brain vacuolation increased, white matter, minimal		--	--	--	--	6

Finding Group (dose mg/kg)		0	10	20	30	45
Primary necropsy, Females	**# examined**	**15**	**15**	**15**	**15**	**8**
Brain vacuolation increased, white matter, minimal		2			3	2
No CNS findings in recovery females						

--: Group not assessed at this timepoint

Summary of Co-occurrence of Death and CNS Findings in High-Dose Rats (13-Week Study)

- 16 of 46 (34.8%) were found dead or euthanized between Days 10 and 58
  - 5 of the 16 (31.3%) had white matter vacuolation
    - 2 of the 5 (40.0%) also had convulsions or tremors
  - 1 of the 16 (6.3%) had tremors without white matter vacuolation
- 8 of the 30 remaining animals also had white matter vacuolation

Data [Summarized by the Applicant]:

A 13-week oral toxicity study with an 8-week recovery period in the monkey / Study 1070417:

Key Study Findings

High dose of 75 mg/kg/day was chosen based on results from 4-week monkey study at doses of 30, 75 and 150 mg/kg/day.

- Minimal decreases in albumin (to 0.71X predose) and total protein as well as 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. In the liver of males at 75 mg/kg/day, there was minimal to mild subcapsular neutrophilic infiltration associated with single cell necrosis.
- All findings are reversible.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	10, 30 and 75 mg/kg, once daily
Route of administration:	Oral (Gavage)
Formulation/Vehicle:	0.5% (w/v) methyl cellulose (400 cps) in ultra-pure water
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	4/sex/group, plus 2/sex in control and high dose
Age:	2-3 years old
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	None
Clinical Signs	Occasional salivation in high-dose
Body Weights	No change
Ophthalmoscopy	No findings
ECG	No findings
Hematology	No findings
Clinical Chemistry	Minimal decreases in albumin (to 0.71X predose) and total protein as well as 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.
Urinalysis	No findings
Gross Pathology	No findings
Organ Weights	No findings

Histopathology	Neutrophic infiltration with single cell necrosis in liver of males in high dose
Other evaluations	None
LD: low dose; MD: mid dose; HD: high dose. -: indicates reduction in parameters compared to control.	

The Applicant's Position:

Repeat-dose toxicity studies conducted in mice, rats, and Cynomolgus monkeys revealed the following target organs or systems: pancreas, brain/CNS, and liver.

The FDA's Assessment:

FDA generally agrees with Novartis's assessment and has included the 13-week monkey TK data for completeness.

Table 9: Toxicokinetic data (13-week study; Monkeys)

Dose level (mg/kg)	Day 28		Day 87	
	AUC_{0-24} (ng*hr/mL)	Exposure multiple	AUC_{0-24} (ng*hr/mL)	Exposure* multiple
Males				
10	6270	0.2	7100	0.2
30	27800	0.7	42300	1.0
75	79800	2.0	119000	2.9
Females				
10	9560	0.2	7310	0.2
30	34100	0.8	23400	0.6
75	66900	1.7	79300	2.0
*AUC_{0-24} at the human clinical dose: 40,400 ng*hr/mL				

General toxicology; additional studies

Data [Summarized by the Applicant]:

A 4-week oral toxicity study with Cynomolgus monkeys with a 4-week recovery period (Study T08-01-08):

In the 28-day monkey study at doses of 0, 30, 75 and 150 mg/kg/day, reversible minimal-to-mild pancreatic acinar cell apoptosis without inflammation was observed for animals in all groups, as well as minimally higher serum amylase values in some high-dose animals. The liver-related changes included slight increases in liver enzymes (ALT, AST). 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. No alterations in kidney function were observed (no effect on serum BUN or creatinine levels or urine parameters).
Follow up investigations on the identity of the crystalline-like material indicated that the material is not capmatinib or its metabolite, but rather calcium phosphate precipitates [Report RD-2015-00175] [Study 1820224]. The relationship of this material to capmatinib treatment is therefore uncertain, as such precipitates are known to occur in untreated monkeys (Cline et al 2012).

FDA Additional Comment on 4-week Monkey Toxicology Study:
For the high dose groups, the average exposure for males and females by AUC was 3.6 and 3.4 times, respectively, the clinical exposure based on AUC at the 400 mg dose twice daily dose. Findings were generally similar to those observed in the 13-week monkey study, with the addition of one pre-term death: a high-dose female that experienced pulmonary edema, cerebral edema, subcutaneous edema, and possible sepsis.

Table 10: Toxicokinetic data (4-week study; Monkeys)

Dose Level (mg/kg)	AUC_{0-24} (µM*hr)	Exposure multiple*
Day 27		
Males		
30	96.7	1.0
75	220	2.2
150	350	3.6
Females		
30	111	1.1
75	263	2.7
150	334	3.4

*AUC_{0-24} at the human clinical dose: 98 µM*hr

The Applicant's Position:
The kidney findings in the 28-day monkey study (deposits of amphophilic, crystalline-like material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen at doses of 75 and 150 mg/kg/day) was not associated with kidney function changes, and was not reproduced in the 13-week monkey study (at doses up to 75 mg/kg/day). The identity of the crystalline-like material indicated that the material is not capmatinib or its metabolite, but rather calcium phosphate precipitates, and possibly a consequence of urinary concentration. The relationship of this material to capmatinib treatment is therefore uncertain.

The FDA's Assessment:

FDA reviewed the 4-week GLP-compliant studies in monkeys and rats at the time of the original IND submission and confirms the Applicant's presentation of the monkey data showing that the major target organs were the CNS based on clinical signs and histopathology and the liver based on changes in clinical chemistry.

In a 4-week GLP-compliant toxicology study in Sprague Dawley rats (Study # T08-04-11), animals received capmatinib at doses of 20, 60, and 120 mg/kg/day for males and 10, 30, and 60 mg/kg/day for females via oral gavage. For the high dose groups, the average exposure for males and females by AUC was 2.8 and 2.2 times, respectively, the exposure based on AUC at the 400 mg dose twice daily clinical dose (Table 11).

Table 11: Toxicokinetic data (4-week study; Rats)

Dose Level (mg/kg)	AUC_{0-24} (µM*hr)	Exposure multiple*
Day 27		
Males		
20	40	0.4
60	143	1.5
120	272	2.8
Females		
10	38	0.4
30	145	1.5
60	214	2.2

*AUC_{0-24} at the human clinical dose: 98 µM*hr

Findings were generally similar to those observed in the 13-week rat study, including dark red discolored lungs, pancreatic acinar cell vacuolation, increased creatinine, amylase, ALT, AST, alkaline phosphatase, and bilirubin and decreased albumin; however, the slightly higher exposure in the 4-week study correlated with a higher incidence of brain lesions (50% vs. 28%) and early death (63% vs. 35%). A low incidence of convulsions/ tremors occurred in the high-dose groups of both the 4 and 13-week studies.

Summary of Co-occurrence of Death and CNS Findings in High Dose Rats (4-Week Study)

- 20 of 30 (66.7%) were found dead or euthanized between Days 4 and 28
  - 12 of the 20 (60.0%) had white matter vacuolation
    - 4 of the 12 (33.3%) also had convulsions or tremors
- 3 of the 10 remaining animals had white matter vacuolation at scheduled sacrifice

5.5.2. Genetic Toxicology

The Applicant's Position:

In the in vitro studies, capmatinib did not induce mutations in the bacterial reverse mutation assay (Study 1070233) and did not cause chromosomal aberrations in the chromosome aberration assay in human peripheral blood lymphocytes (Study1070418).
In the in vivo bone marrow micronucleus test in rats (Study 1170161), capmatinib did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats treated up to 200 mg/kg/day (above the MTD) or females treated up to 70 mg/kg/day (an estimate of the MTD).
Based on the in vitro and in vitro results, capmatinib is not mutagenic or clastogenic, thus is not genotoxic.

The FDA's Assessment:

FDA confirmed the Applicant's presentation of the results of the submitted genotoxicity assays and agrees with the conclusions.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title / number: Reverse Mutation in five histidine-requiring strains of *Salmonella typhimurium* / 1070233

Key Study Findings:

- Capmatinib was not mutagenic in five *Salmonella typhimurium* strains in the presence or absence of S9 activation.
- Standard positive controls confirmed the sensitivity and validity of the assay.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA97a, and TA102; capmatinib tested up to 5000 µg/plate; +/- S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title / number: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes / 1070418

Key Study Findings:

- Capmatinib did not induce chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of S9 activation.

- The performance of the positive controls confirmed the sensitivity and validity of the study.

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes; capmatinib up to 150 µg/mL; +/- S9; (positive control in the absence of S9: 5 µg/mL 4-nitroquinoline 1-oxide; positive control in the presence of S9: 6.25 µg/mL cyclophosphamide).
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title / number: Induction of micronuclei in the bone marrow of treated rats/ 1170161

Key Study Findings:

- Capmatinib did not induce a significant increase in rat micronucleated bone marrow polychromatic erythrocytes compared to the vehicle control.
- The performance of the positive control confirmed the sensitivity and validity of the study.

GLP compliance: Yes
Test system: Rats, given capmatinib (17.5, 35 and 70 mg/kg/day for females; 50, 100 and 200 mg/kg/day for males) by oral gavage on Days 1 and 2; (positive control: single oral dose of 20 mg/kg cyclophosphamide)
Study is valid: Yes

Other Genetic Toxicity Studies *(For API only; does not refer to impurities)*
None.

The FDA's Assessment:
None.

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted with capmatinib (consistent with ICH S9 guidance).

The FDA's Assessment:
No comment

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Data [Provided by the Applicant]:
No fertility studies were conducted. There were no histopathological findings in reproductive organs in repeated dose toxicity studies in rats and monkeys.

The FDA's Assessment:
FDA agrees that there were no effects on male and female reproductive organs in general toxicology studies conducted in rats and monkeys at doses resulting in exposures of up to approximately 3.6 times the human exposure (AUC) at the 400 mg twice daily clinical dose.

Embryo-Fetal Development
Data [Presented by the Applicant]:
An oral (gavage) embryo-fetal development study in rats / Study 1170160
Key Study Findings*:*

- Dose dependent reduction in maternal body weight gain and food consumption at 30 mg/kg/day. There were no capmatinib-related macroscopic findings at any dose level for the dams.
- Decreased fetal weights, and Increased incidences of litters and fetuses with malformations were noted at doses ≥ 10 mg/kg/day (with maternal systemic exposure at 0.56 times the exposure in humans at the MRHD of 400 mg bid)
- NOAEL for embryofetal development = 1.0 mg/kg/day (with maternal systemic exposure at 0.04 times the exposure in humans at MRHD of 400 mg bid)

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	1, 10 and 30 mg/kg/day, once daily
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% (w/v) methylcellulose 400 cps in ultra-pure water
Species/Strain:	Rat / Sprague Dawley
Number/Sex/Group:	22 females/group
Satellite groups:	TK animals: 3 females for control, 5 females per treatment group

Study design:	Dosed from day 6 to 17 postcoitum (pc), TK (maternal) on day 17 pc, C-Section on day 21 pc,
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	Reduced body weight gain at 30 mg/kg
Necropsy findings Cesarean Section Data	LD: No macroscopic findings MD: No macroscopic findings HD: No macroscopic findings

FDA Additional Data: Rat Cesarean Section Data

Table 12: Cesarean Section Data (EFD study; Rats)

mg/kg/day	0	1	10	30
Exposure multiple		0.04 X	0.56 X	1.4 X
Pregnancy index (%)	91.7%	95.8%	91.7%	91.7%
# Females w/ viable fetuses for Day 21 exam	22	22	23	22
Number pregnant	22	22	23	22
Number not pregnant	2	2	1	2
Mean gravid uterine weight (g)	105.0	99.8	93.9	85.5
Mean corpora lutea	15.8	15.9	16.1	15.0
Mean implantation sites	14.1	13.7	14.7	13.9
Mean % preimplantation loss	10.8%	13.6%	8.6%	7.8%
Mean % postimplantation loss	3.2%	2.6%	5.4%	5.2%
Mean early resorptions	0.4	0.3	0.7	0.7
Mean late resorptions	0	0	0.1	0
Mean live fetuses	13.7	13.4	13.8	13.1
% Males	42.3%	52.2%	52.5%	46.4%
Mean weight of males (g)	6.02	5.83	5.18*	4.60*
% change from control		↓3.2%	↓14.0%	↓23.6%
Mean weight of females (g)	5.70	5.50	4.91*	4.32*
% change from control		↓3.5%	↓13.9%	↓24.2%

Note: All fetuses were viable * Significantly different from control group (p≤0.001)

Applicant Presentation

Necropsy findings Fetal/ Offspring	LD: No effects (NOAEL)

	MD: Decreased fetal weights; Increased incidences of litters and fetuses with malformations (e.g., abnormal flexure of forepaws/hindpaws, inward malrotation of hindpaws/forepaws, thinness of the forelimbs and lack/reduced flexion at the humerus/ulna joints). HD: Including findings in MD, plus narrowed and/or small tongue and irregular ossification of the fibula parallel with the tibia.

Fetal findings

Daily dose (mg/kg/day)	0 (Control)	1	10	30
Litters No. litters evaluated:	22	22	23	22
Fetal malformations: Total affected fetuses (litters)[a]:				
Gross external malformations:				
narrowed tongue	0 (0)	0 (0)	0 (0)	247 (21)
small tongue	0 (0)	0 (0)	0 (0)	189 (21)
abnormal flexure of forepaw(s)	0 (0)	0 (0)	310 (23)	284 (22)
abnormal flexure of hindpaw(s)	0 (0)	0 (0)	9 (3)	257 (22)
inward malrotation of hindpaw(s)	0 (0)	1 (1)	5 (3)	208 (21)
inward malrotation of forepaw(s)	0 (0)	0 (0)	291 (23)	269 (22)
entire length of forelimb(s) thin	0 (0)	0 (0)	290 (23)	286 (22)
entire length of hindlimb(s) thin	0 (0)	0 (0)	36 (6)	285 (22)
lack of flexion at humerus/ulna joints	0 (0)	0 (0)	11 (4)	108 (18)
reduced flexion at humerus/ulna joints	0 (0)	0 (0)	58 (10)	156 (22)
Visceral malformations (litters):	-	-	-	-
Skeletal malformations (litters):				
fibula irregular ossification parallel with tibia	0 (0)	0 (0)	5 (2)	143 (22)

- = no noteworthy findings;
[a] = test item-related malformations are listed.

LD: low dose; MD: mid dose; HD: high dose

FDA Additional Comment on Rat Embryo-Fetal Toxicity Data:

Malformations occurred in 4.5%, 100%, and 100% of litters at the 1, 10, and 30 mg/kg dose levels, respectively. In addition to the malformations listed above, malformations of abnormal flexure and inward malrotation of limbs occurred less frequently.

Table 13: Toxicokinetic data: maternal plasma (EFD study; Rats)

Dose Level (mg/kg)	AUC_{0-24} (ng*hr/mL)	Exposure multiple*
Day 17		
1	1810	0.04
10	22700	0.56
30	56300	1.4

*AUC0-24 at the human clinical dose: 40,400 ng*hr/mL

The Applicant's Position:

The NOAEL for maternal toxicity was considered to be 10 mg/kg/day. The NOAEL for embryo-fetal development was considered to be 1 mg/kg/day. Capmatinib is teratogenic in the rat.

Data [Presented by the Applicant]:

An oral (gavage) embryo-fetal development study in rabbits / Study 1170159

Key Study Findings

- There were no treatment-related adverse maternal effects at any dose level
- Small lung lobes and fusion of lung lobe were observed in one fetus at 5 mg/kg/day (with systemic exposure at 0.016 times the exposure in humans at the therapeutic dose of 400 mg BID), Reduced fetal weight, malformations (mainly affecting the limbs) in all litters at 60 mg/kg (with systemic exposure at 1.5 times the exposure in humans at the therapeutic dose of 400 mg BID).
- NOAEL for fetal development = 1 mg/kg/day (with systemic exposure at 0.001 times the exposure in humans at the therapeutic dose of 400 mg BID

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	1, 5 and 60 mg/kg, once daily
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% (w/v) methylcellulose 400 cps in ultra-pure water
Species/Strain:	Rabbit / New Zealand White
Number/Sex/Group:	20 females/group
Satellite groups:	3 females in control; 5 females / treatment group
Study design:	Dosing: Day 7-20 pc; TK (maternal): day 20 pc; C-section: day 29 pc.

Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	No changes
Necropsy findings Cesarean Section Data	LD: No macroscopic findings MD: No macroscopic findings HD: No macroscopic findings

FDA Additional Comment on Rabbit Cesarean Section Data:

Minor decreases in fetal weight occurred at the high dose; the decrease was statistically significant in females.

Table 14: Cesarean Section Data (EFD study; Rabbits)

mg/kg/day	0	1	5	60
Exposure multiple		0.001 X	0.016 X	1.5 X
Pregnancy index (%)	100%	95%	95%	100%
# Females w/ viable fetuses for Day 21 exam	20	19	19	20
Number pregnant	20	19	19	20
Number not pregnant	0	1	1	0
Mean gravid uterine weight (g)	497.8	468.8	493.3	459.8
Mean corpora lutea	9.6	9.2	9.9	9.4
Mean implantation sites	9.1	8.2	9.1	8.7
Mean % preimplantation loss	5.2%	10.0%	9.2%	8.4%
Mean % postimplantation loss	3.2%	3.7%	7.9%	2.4%
Mean early resorptions	0.3	0.2	0.7	0.2
Mean late resorptions	0.1	0.1	0.1	0.1
Mean live fetuses	8.8	7.9	8.3	8.4
% Males	53.4%	49.6%	45.7%	42.3%
Mean weight of males (g)	40.9	43.9	43.0	38.6
% change from control		↑7.3%	↑5.1%	↓5.6%
Mean weight of females (g)	41.1	42.1	42.6	37.8*
% change from control		↑2.4%	↑3.6%	↓8.0%

Note: All fetuses were viable

* Significantly different from control group (p≤0.001)

Applicant Presentation

Necropsy findings Fetal/ Offspring	LD: No fetal findings

[malformations, variations, etc.]	MD: Malformations including small lung lobes and fusion of lung lobe in one fetus HD: Reduced fetal weights and malformations in all litters/fetuses (mainly affecting the limbs, also with tongue and lung).

Fetal Findings

Daily dose (mg/kg/day)	0 (Control)	1	5	60
Litters evaluated	20	19	19	20
Fetal malformations: Total affected fetuses (litters) [a]:				
Gross external malformations:				
narrowed tongue	0 (0)	0 (0)	0 (0)	153 (20)
small tongue	0 (0)	0 (0)	0 (0)	115 (19)
abnormal flexure of hindpaw(s)	0 (0)	0 (0)	0 (0)	168 (20)
inward malrotation of forepaw(s)	0 (0)	0 (0)	0 (0)	128 (19)
inward malrotation of hindpaw(s)	0 (0)	0 (0)	0 (0)	90 (19)
outward malrotation of hindpaw(s)	0 (0)	0 (0)	0 (0)	38 (14)
entire length of forelimb(s) thin	0 (0)	0 (0)	0 (0)	167 (20)
entire length of hindlimb(s) thin	0 (0)	0 (0)	0 (0)	118 (15)
lack of flexion at humerus/ulna joints	0 (0)	0 (0)	0 (0)	61 (12)
reduced flexion at humerus/ulna joints	0 (0)	0 (0)	0 (0)	113 (17)
Visceral malformations:				
small lung lobes	0 (0)	0 (0)	1 (1)	118 (20)
Skeletal malformations:				
ulna irregular ossification adjacent to humerus/ulna joint	0 (0)	0 (0)	0 (0)	168 (20)
ulna misaligned slightly shifted parallel with radius	0 (0)	0 (0)	0 (0)	168 (20)
fibula irregular ossification parallel with tibia	0 (0)	0 (0)	0 (0)	168 (20)

- = no noteworthy findings;
a = test item-related malformations are listed.

LD: low dose; MD: mid dose; HD: high dose

FDA Additional Comment on Rabbit Embryo-Fetal Toxicity Data:

Malformations occurred in 5.3%, 15.8%, and 100% of litters at the 1, 5, and 60 mg/kg dose levels, respectively.

FDA Additional Data: Rabbit Toxicokinetic Data

Table 15: Toxicokinetic data: maternal plasma (EFD study; Rabbits)

Dose Level (mg/kg)	AUC0-24 (ng*hr/mL)	Exposure multiple*
Day 20		
1	48.6	0.001
5	630	0.016
60	59400	1.5

*AUC0-24 at the human clinical dose: 40,400 ng*hr/mL

The Applicant's Position:
NOAEL for maternal toxicity is 60 mg/kg/day; NOAEL for embryofetal development is 1 mg/kg/day; Capmatinib is teratogenic to rabbits.

The FDA's Assessment:
FDA confirmed the Applicant's data and generally agrees with the Applicant's assessment. In both species there was little maternal toxicity and clear malformations at maternal exposures that were lower than the clinical exposure at the 400 mg twice daily dose.

Prenatal and Postnatal Development
No studies conducted.

The FDA's Position:
Pre- and postnatal development studies were not conducted or necessary to support an indication for patients with advanced cancer.

5.5.5. Other Toxicology Studies

Data:

Photosafety:
Capmatinib was assessed for potential phototoxicity by in vitro Neutral Red Uptake assay (Study 1170662) and in vivo local lymph node assay (Study 1370074). Capmatinib demonstrated phototoxic potential in both studies.

Impurity qualifications:
A series of in vitro and in vivo studies were conducted to qualify for impurities (b) (4) and (b) (4), for which specifications were set at (b) (4), respectively. The materials tested in

these studies were capmatinib drug substance spiked with impurities (b) (4) at various levels.

In the Ames test (Study 1570058) and in vitro chromosome aberration assay (Study 1770826) with capmatinib batch 15/1 (with impurities: (b) (4), there was no evidence of increased mutations in the bacterial strains tested, but there was increased structural chromosome aberrations in cultured human peripheral blood lymphocytes. In a follow up in vivo micronucleus test and alkaline Comet assay (Study 1870270), capmatinib batch 18/1 (with impurities: (b) (4), did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of male and females rats treated up to 70 mg/kg/day (estimated MTD), nor did it cause DNA strand breaks in the liver at the same dose. Based on weight-of-evidence approach, the impurities are considered not genotoxic, and considered qualified at the proposed limits.

In a 4-week rat impurity qualification study (Study 1570059), the findings in animals treated with capmatinib at doses of 10 and 30 mg/kg/day (females) or at doses of 20 and 60 mg/kg/day (males) with impurities (b) (4) were in general, comparable to those in animals given capmatinib at a dose of 30 (females) and 60 mg/kg/day (males) with impurity (b) (4) only. Irrespective of the presence of impurities, findings in the impurity qualification study in rats were generally comparable to earlier toxicity studies conducted for capmatinib, indicating that the presence of impurities (b) (4) (b) (4) did not change the toxicity profile of capmatinib.

Applicant's Position:

The impurities (b) (4) are considered qualified at the proposed specifications (b) (4).

The FDA's Assessment:

FDA agrees that impurities (b) (4) are considered qualified at the proposed specifications. Capmatinib demonstrated in vitro phototoxic potential in a 3T3 Neutral Red Uptake assay (Study 1170662; chlorpromazine positive control PIF: 12.5; capmatinib PIF: 48.2). Capmatinib also demonstrated in vivo phototoxic potential in an ultraviolet local lymph node assay in BALB/c mice (Study 503091; phototoxic effect at (b) (4) mg/kg = C_{max} of (b) (4) ng/mL).

Claire E. Myers, Ph.D.
Primary Reviewer

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Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Capmatinib is an oral tyrosine kinase inhibitor intended for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a mesenchymal-epithelial transition (MET) exon 14 skipping mutation as detected by an FDA-approved test. The proposed dosing regimen is 400 mg orally twice daily (BID) with or without food.

The clinical efficacy of capmatinib is demonstrated in Cohort 4 and Cohort 5b of Study CINC280A2201 (A2201) with the overall response rate (ORR) of 41% in patients who had one or two prior lines of therapy (Cohort 4, N=69) and 68% in treatment-naïve patients (Cohort 5b, N=28) with MET mutated NSCLC following 400 mg capmatinib tablets BID. Exposure-efficacy relationship for best overall response (BOR), duration of response (DOR) or tumor size change from baseline showed a relative flat curve in Cohort 4 and Cohort 5b; however, this relationship was inconclusive due to small number of patients. The safety profile of the proposed dosage of capmatinib 400 mg BID is considered acceptable and managed in the clinical studies. A trend in increased incidences of all grades of nausea/vomiting, abnormalities in lipase and amylase laboratory values and peripheral edema with increased exposure was observed.

The recommendation of administering capmatinib without regard to food is supported by the food effect study (CINC280X2107) showing that a low-fat meal had no clinically significant effect on capmatinib exposure and the comparable safety profile between patients who had no food restriction and those under modified fasting conditions in Study A2201. The dedicated hepatic impairment study (CINC280A2106) found no effect of mild, moderate and severe hepatic impairment on capmatinib exposure. The effect of renal impairment on capmatinib exposure is expected to be minimal due to negligible capmatinib (unchanged) renal excretion. Therefore, dose adjustment is not recommended in patients with varying degrees of hepatic or renal impairment. No large mean increase in QTc (i.e. > 20 ms) was detected at the recommended dose of 400 mg capmatinib BID.

The review team recommends closely monitoring patients for increased adverse events during concomitant use of capmatinib with strong CYP3A inhibitors given that itraconazole increased capmatinib exposure by 42% in a drug-drug interaction (DDI) study (CINC280A2102) and the safety profile beyond the dose of 400 mg capmatinib tablet BID has not been evaluated. The review team also recommends avoidance of coadministration of capmatinib with strong or moderate CYP3A inducers as rifampicin decreased capmatinib exposure by 67% in a DDI study

(CINC280A2102) and efavirenz is predicted to decrease capmatinib exposure by 44%. In addition, if coadministration is unavoidable with certain CYP1A2 substrates, P-gp or BCRP substrates, and MATEs substrates (MATE1 and MATE2K) where minimal concentration changes may lead to serious adverse reactions, decrease the dosage of the substrates in accordance with the approved prescribing information. This recommendation is based on the data that capmatinib increased the exposure of caffeine, digoxin and rosuvastatin by 134%, 47% and 108%, respectively and in vitro data showed a high inhibition risk for concomitant use of MATEs substrates with capmatinib.

Recommendations: The Clinical Pharmacology review team has reviewed the information contained in NDA 213591. This NDA is approvable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	In the pivotal Study A2201 in patients with MET exon 14 skipping mutation NSCLC following 400 mg capmatinib tablets BID, a 41% (95% CI: 29%, 53%) ORR was achieved in the pretreated setting (Cohort 4) and a 68% (95% CI: 48%, 84%) ORR was achieved in the first line setting (Cohort 5b).
General dosing instructions	The proposed capmatinib dosage of 400 mg BID taken with or without food is acceptable for approval based on the following: • This dosage regimen has been demonstrated to be efficacious in the pivotal Study A2201. • The safety and tolerability profile of capmatinib is considered acceptable and manageable in Study A2201, all NSCLC patients and all solid tumor patients. • Administration of capmatinib without regard to food is supported by no effect of a low- fat meal on capmatinib exposure and the comparable safety profile between patients who had no food restriction and those under modified fasting conditions in Study A2201. • The exposure-response analysis for efficacy showed a relative flat curve between capmatinib C_{max} or C_{avg} and efficacy endpoints in cohort 4.

Dosing in patient subgroups (intrinsic and extrinsic factors)	• Avoid concomitant use with strong and moderate CYP3A inducers when taking capmatinib. • Closely monitor patients for toxicities when concomitantly using capmatinib with strong CYP3A inhibitors. • No dose adjustment is recommended for patients with mild, moderate or severe hepatic impairment. • No dose adjustment is recommended for patients with mild or moderate renal impairment. Although capmatinib has not been studied in patient with severe renal impairment, dose adjustment is not expected in this subpopulation given the renal excretion of the unchanged capmatinib is negligible. • If coadministration is unavoidable with certain CYP1A2 substrates, P-gp or BCRP substrates, and MATEs substrates where minimal concentration changes may lead to serious adverse reactions, decrease the dosage of the substrates in accordance with the approved prescribing information.
Bioavailability between the capsules and tablets used in clinical studies	In Study X2102, the ratio of capmatinib 400 mg tablet BID to 600 mg capsule BID for $AUC_{0\text{-}12hr,ss}$ and $C_{max,ss}$ is 0.98 and 1.2, respectively.

Labeling	Following are recommended in the proposed labeling • Closely monitor patients for toxicities during concomitant use of TABRECTA with strong CYP3A inhibitors • Avoid coadministration of TABRECTA with strong and moderate CYP3A inducers. • If coadministration is unavoidable with CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information. • If coadministration is unavoidable with P-gp and BCRP substrates where minimal concentration changes may lead to serious adverse reactions, decrease the P-gp or BCRP substrate dosage in accordance with the approved prescribing information. • If coadministration is unavoidable with MATE1 and MATE2K substrates where minimal concentration changes may lead to serious adverse reactions., decrease the MATE1 or MATE2K substrate dosage in accordance with the approved prescribing information.

Post-Marketing Requirements and Commitments: None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data and The Applicant's Position:

A comprehensive clinical pharmacology program was conducted with capmatinib. The PK of capmatinib was well characterized in healthy subjects and in cancer patients following single dose and/or multiple doses, and with population PK analysis in patients. The dedicated clinical pharmacology studies in healthy subjects or in patients (human ADME, victim and perpetrator DDI for CYPs and transporters, PPI, food effect and hepatic impairment) together with in vitro studies using human biomaterials were conducted and integrated to characterize the ADME properties of capmatinib and assess the impact of intrinsic and extrinsic factors on the PK of capmatinib, which are sufficient to inform the proper use of capmatinib and to support the proposed label. In addition, results from both exposure-efficacy analyses in MET mutation

cohorts in pivotal study and exposure-safety analyses (including concentration-QTc analysis) using pooled data from multiple single agent studies in patients together with efficacy and safety data supported the recommended dose of 400 mg capmatinib, orally, twice daily.

The FDA's Assessment:
In general, FDA agrees with the Applicant's assessment on the clinical pharmacology and pharmacokinetics (PK) of capmatinib. However, FDA does not agree with the Applicant's assessment regarding the (b) (4) See FDA's assessment in the sections below.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
The recommended phase 2 dose (RP2D) of 400 mg b.i.d. for capmatinib tablet formulation was based on the results from Study INC280X2102 (referred to as Study X2102 here after) conducted in subjects with advanced MET-dysregulated solid tumors.

The starting dose in Study X2102 was 100 mg b.i.d. in capsules, which was then escalated through multiple dose levels to 600 mg b.i.d. with the capsule formulation. No further dose escalation beyond 600 mg b.i.d. with the capsule formulation was conducted as data from Study X1101 indicated that exposure did not increase beyond 600 mg, likely due to the saturation of absorption for the capsule formulation. Based on the preliminary safety, pharmacodynamic, and efficacy data, the recommended Phase II dose (RP2D) was declared as 600 mg b.i.d. for the capsule formulation.
A tablet formulation was subsequently developed and introduced into Study X2102 at the 400 mg b.i.d. dose level. The data showed 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.. The capsule and tablet pharmacokinetic (PK) data from Study X2102 were used to bridge the selection of the tablet RP2D as 400 mg b.i.d.. The maximum tolerated dose was not reached with either the capsule or tablet formulation.
Overall, the following safety, efficacy, and pharmacodynamic data were considered for the RP2D selection:

- Safety data indicated that capmatinib was well tolerated at 600 mg b.i.d. for capsules and 400 mg b.i.d. for tablets following multiple cycles of treatment. Most of the AEs suspected to be related to the study drug (by the Investigator) were CTCAE grade 1 or 2.

- Clinical activity was observed at 600 mg b.i.d. for capsules or 400 mg b.i.d. for tablets in subjects with MET-dysregulated NSCLC: 12 of 55 subjects (23.6%) in the expansion phase had CR or PR. Among them, 7 of 15 subjects with NSCLC (53.3%) with MET amplified (gene copy number (GCN) ≥ 6) NSCLC) treated at the RP2D had responses determined to be CR or PR. Among these subjects, 3 out of 4 subjects whose NSCLC harbored MET mutation(s) also achieved a confirmed CR or PR.
- Pharmacodynamic data showed that 1 subject (with advanced colorectal cancer) had near-complete phospho-MET inhibition at 450 mg b.i.d. with capsules, and 2 subjects with NSCLC in the expansion phase had phosphorylated MET inhibition of 95%.
- Consistent with observed clinical pharmacodynamic data, the capmatinib steady-state plasma trough concentration at 600 mg b.i.d. capsules and 400 mg b.i.d. tablets were well above the IC95 (132 ng/mL) for MET inhibition derived from the S114 mouse allograft model. Therefore, it is expected that constant target inhibition could be achieved during the dosing interval at these RP2Ds. Twice-daily dosing is required to maintain the concentration above this threshold during the dosing interval.

Clinical results from Study A2201 together with exposure-response analyses, both for efficacy and safety, further support the recommended dose of 400 mg b.i.d.. All patients enrolled in the A2201, including those from the MET mutated cohorts which represent the basis for this NDA submission, were treated at the dose of 400 mg b.i.d. The MET mutated cohorts patients from A2201 were included in the exposure-efficacy analysis. The exposure-safety analysis was conducted using pooled data from all patients at all dose levels in studies A2201, A2108, X1101 and X2102.

Robust efficacy was observed with the dose of 400 mg b.i.d. for capmatinib tablets in subjects with MET mutated NSCLC, where a 67.9% ORR and (95% CI: 47.6, 84.1) and 11.14 months (95% CI: 5.55, not estimable) DOR was achieved for the first line patients and 40.6% ORR (95% CI: 28.9, 53.1), 9.72 months (95% CI: 5.55, 12.98) months DOR in the pretreated setting. Exposure-efficacy analyses showed no relationship between capmatinib exposure and efficacy endpoints BOR, DOR, or tumor size change from baseline in pretreated or treatment naïve patients, while the relationship was inconclusive for exposure-PFS analysis. The lack of a clear exposure-efficacy relationship could be due to small sample size (67 subjects in Cohort 4 and 27 subjects in Cohort 5b) with a single dose level in study A2201. Nevertheless, 400 mg b.i.d. was expected to be sufficient to maintain constant target inhibition. A human equivalent IC95 (132 ng/mL) for phospho-MET inhibition was derived by PK/PD analysis using data from mouse S114 allograft model and corrected for plasma protein binding difference between mouse and human. Based on population PK simulations, 96% (90% CI: 94%, 98%) of patients have steady state capmatinib plasma concentration above IC95 for MET inhibition during the dosing interval with 400 mg b.i.d regimen.
At dose of 400 mg b.i.d, capmatinib showed manageable safety profile with the majority of

the adverse events being grade 1 and 2. Exposure-safety analyses conducted on pooled data from single agent studies showed a positive association between capmatinib exposure and all grades of nausea/vomiting, abnormalities in lipase and amylase laboratory values. A positive but weak relationship was also observed between capmatinib exposure and all grades of peripheral edema. Concentration-QTc analysis has demonstrated an absence of clinically significant QTc prolongation at the therapeutic concentrations. It is noteworthy the incidence rate of grade 3 or 4 events (irrespective of study treatment) were low for peripheral edema (5.7%), lipase increased (4.3%), amylase increased (3.3%), nausea (2.8%) and, vomiting (2.8%). Therefore, the positive association identified between capmatinib exposure and these safety endpoints is largely driven by the low-grade cases. And the proposed dose modifications for capmatinib is appropriate for the AE management.

The Applicant's Position:

The clinical efficacy and safety data as well as exposure-response analyses support the recommended 400 mg b.i.d. dose of capmatinib used to treat MET-mutated NSCLC.

The FDA's Assessment:
FDA concurs with the Applicant's position.

The results of the dose escalation and dose expansion Study X2102 supported the selection of capmatinib capsule 600 mg BID to be evaluated in the phase 2 setting. The PK bridging data between 600 mg BID capsule and 400 mg BID tablet in the same study supported the selection of tablet 400 mg BID as the recommended phase 2 dose (RP2D).

The efficacy of the proposed dosing regimen of capmatinib tablet 400 mg BID has been demonstrated in Study A2201 and supported by efficacy data in Study X2102 in the intended patient populations. The exposure-efficacy analyses showed a trend of flat curve between capmatinib C_{max} or C_{avg} and efficacy endpoints in cohort 4 and 5b but the number of patients is limited. Population PK simulation predicted that 96% of the patients with capmatinib 400 mg BID would have steady state trough concentrations above IC95 for MET inhibition, indicating that the proposed dosing regimen of capmatinib should maintain the pharmacodynamic effect constantly during the treatment duration to achieve the clinically efficacy.

The safety profile in Study A2201 and in a pooled analysis of all NSCLC patients and all solid tumor patients showed that the proposed dosage of 400 mg BID is tolerable and managed with the majority of the adverse events being grade 1 and 2. Exposure-safety analyses suggest higher capmatinib concentration were associated with increased risk of nausea/vomiting events of any grade, as well as newly occurred all grades of abnormalities in levels of lipase and amylase. A trend of higher grade 3-4 abnormalities in levels of amylase in patients with higher

capmatinib exposure was also observed, but the slope appears to be very shallow. Similar trend was not identified for grade 3+ abnormalities in levels of lipase or grade 3+ nausea/vomiting.

Overall, the benefit-risk assessment demonstrates that the proposed dosage of capmatinib tablet 400 mg BID has clinical benefit in the intended population as a general dosing recommendation.

6.2.2.2. Therapeutic Individualization

Data:

Pharmacokinetics in subjects with impaired hepatic and renal function
Impaired hepatic function: Results from Study A2106 showed that AUCinf was 23% and 9% lower in the mild and moderate groups, respectively, while the AUCinf in the severe group was 24% higher compared to the normal group. Cmax was 28% and 17% lower, respectively, in the mild and moderate hepatically impaired groups while remaining similar in the severe group compared to the normal group.

Impaired renal function: The population PK analysis included 207 subjects with normal renal function (creatinine clearance (CLcr) ≥ 90 mL/min), 200 subjects with mild renal impairment (CLcr 60 to 89 mL/min), and 94 subjects with moderate renal impairment (CLcr 30 to 59 mL/min). The CLcr had no statistically significant effect on CL/F of capmatinib. No significant difference in the simulated steady-state AUC0-12h was shown for the mildly, geometric mean ratio of 0.99 (90%CI: 0.88, 1.11), or moderately, geometric mean ratio of 0.96 (90%CI: 0.82, 1,14), impaired renal function group as compared to the group with normal renal function.

Pharmacokinetics in subpopulation: Population PK analysis showed that gender and age had no statistically significant effect on capmatinib PK.

Body weight was identified to be a statistically significant covariate for capmatinib clearance (CL/F) and volume of distribution (Vc/F). However, the difference in exposure (AUC and Cmax) was within 25% for low body weight subjects (< 60 kg) or high body weight subjects (>80 kg) compared to exposure in reference subjects with body weight 60-80 kg. The body weight effect size was small relative to the high inherent variability in capmatinib PK (inter-patient variability for Cmax and AUCtau are 37% and 43%) .Therefore, no dose adjustment based on body weight was needed, as the difference in exposure was not considered clinically relevant.

Asian race was identified as a statistically significant covariate for CL/F with a factor of 0.899 (95% Confidence interval (CI): 0.801, 0.971 excludes 1) as compared to non-Asian. The geometric mean ratios (GMR) for simulated Cmax and AUC at steady state were 1.04 (90% CI: 0.94, 1.15) and 1.11 (90% CI: 0.97, 1.25), respectively, with 400 mg b.i.d. comparing Asian to non-Asian while holding other covariates the same. The impact of Asian race is therefore not

considered clinically relevant. Japanese (n = 88) vs non-Japanese (n = 413) subjects had no statistical nor clinical significant effect on the PK of capmatinib.

The Applicant's Position:

No dose adjustments are recommended in subjects with mild to moderate renal impairment, or in subjects with mild, moderate, or severe hepatic impairment. Capmatinib has not been studied in subjects with severe renal impairment.
Population PK analysis showed that gender, age, race, body weight, and ethnicity had no clinically relevant effect on capmatinib exposure. So no dose adjustments are warranted in these subpopulations.

The FDA's Assessment:
FDA agrees with the Applicant's position that no therapeutic individualization is needed in patients with mild, moderate or severe hepatic impairment (Child-Pugh classification) or in patients with mild or moderate renal impairment. Given that renal excretion of capmatinib is negligible, a dedicated study to evaluate the effect of severe renal impairment on the PK of capmatinib is not required.

FDA agrees with the Applicant's position that no dose adjustment is needed in any of the subpopulation including sex, age, race, body weight and ethnicity based on the results of the population PK analyses. See Pharmacometrics review for details.

6.2.2.3. Outstanding Issues

The Applicant's Position:

None

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

An overview of ADME properties and clinical pharmacokinetics of capmatinib are provided below.
Absorption: Capmatinib was rapidly absorbed after oral administration in humans. The median time to peak plasma concentrations (Tmax) ranged from 1 to 2 h for tablets and from 1 to 4 h

for capsules after a single treatment dose. In the human ADME study (Study X2106) with the capsule formulation, the extent of oral absorption was estimated to be 49.6% (n = 6). The absorption for tablets was estimated to be higher (> 70%) based on the exposure comparison between the capsule and tablet formulations.
Capmatinib is considered as a BCS class II compound (high permeability and low solubility). The solubility is pH-dependent.

Distribution: Protein binding of capmatinib in human plasma is high, with 96% bound to human plasma proteins independent of concentration in the range tested (from 100 ng/mL to 10000 ng/mL). The in vitro blood-to-plasma ratio was 1.5 (concentration range of 10 ng/mL - 1000 ng/mL) but decreased at higher concentrations to 0.9 (i.e. concentration 10000 ng/mL) indicating a saturation of distribution into red blood cells. The apparent mean volume of distribution at steady state (Vss/F) was 164 L in subjects with cancer based on the population PK analysis.

Metabolism: The human ADME study and in vitro phenotyping results indicated that capmatinib was cleared mainly through metabolism driven by cytochrome P450 (CYP) 3A4 (CYP3A4) and aldehyde oxidase (AO). In the human ADME study, the most abundant radioactive component in plasma was unchanged capmatinib (42.9% of radioactivity AUC0-12h). The metabolite M16 (CMN288), which is pharmacologically inactive, was the major circulating metabolite and accounted for 21.5% of the radioactivity in plasma (AUC0-12h), followed by metabolites M8 and M28, each accounting on average for 5.4% - 5.9% of the plasma radiolabeled [^{14}C]-capmatinib AUC0-12h. Other minor metabolites (M18, M26, and M13) accounted for less than 3% of the plasma [^{14}C] AUC0-12h. The cellular IC50 for MET inhibition for metabolites M8 and M18 was 52-fold lower and 2.5-fold lower than that of capmatinib, respectively. Taking into account their plasma exposure relative to capmatinib, the contribution of both metabolites to total pharmacological activity in human is negligible.

Excretion/elimination: Following oral administration of capsules, capmatinib is eliminated mainly through metabolism, and subsequent fecal excretion. In feces, 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.

Clinical Pharmacokinetics: Capmatinib was rapidly absorbed after oral administration with the median Tmax ranging from 1 to 2 h for tablets and from 1 to 4 h for capsules independent of dose. Capmatinib achieved steady state by the third day following twice-daily dosing. Accumulation of capmatinib following repeated administration of 400 mg b.i.d. tablets is low, with geometric mean accumulation ratio of 1.39-fold. 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 cancer patients. The effective half-life following 400 mg twice daily dosing (b.i.d.) with tablets was 6.54 h. The geometric mean steady state apparent clearance was 19.8 L/h.

Capmatinib exposure with capsules increased with dose up to 600 mg q.d. and 600 mg b.i.d. The systemic exposure with tablet increased dose proportionally from 200 to 400 mg b.i.d. in patients, and from 200 mg to 600 mg following single dose in healthy subjects. No time-dependent PK was observed. Following 400 mg b.i.d. dosing with tablets, the intra- and inter-subject variability (CV%) for AUC0-12h was 30.1% and 55.9%, respectively; for Cmax, it was 34.0% and 53.5%, respectively.

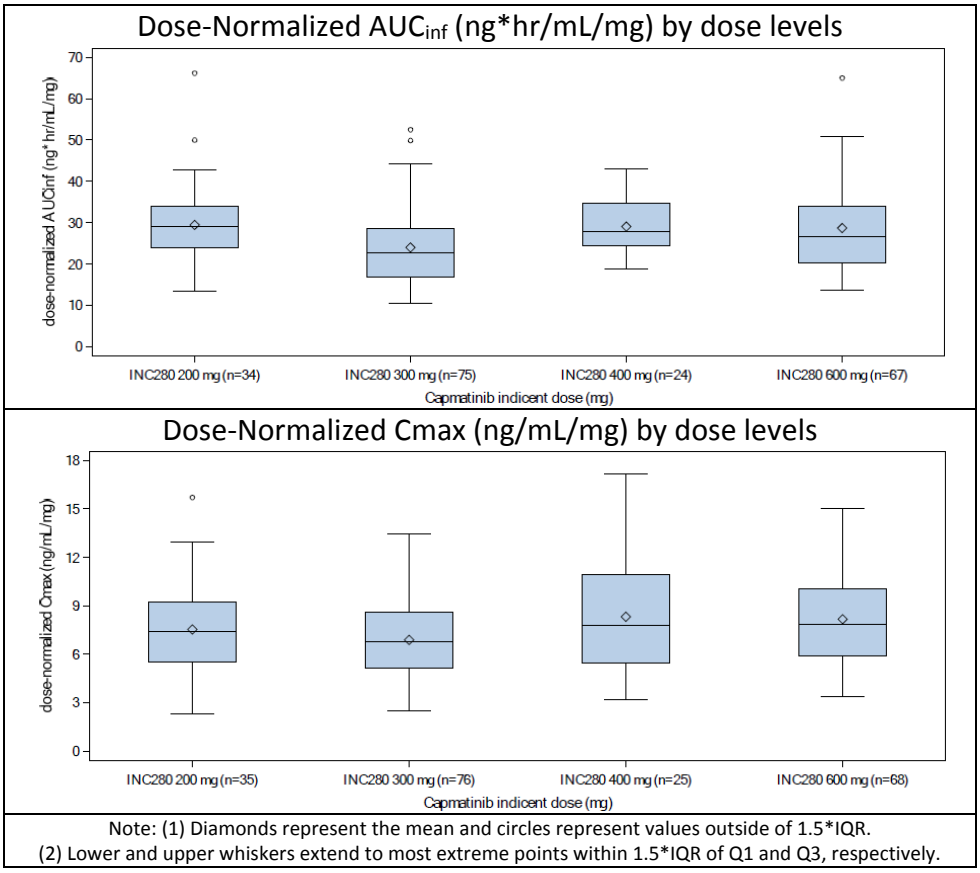
The Applicant's Position:

The clinical PK and ADME properties of capmatinib have been well characterized.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the clinical PK and ADME properties of capmatinib have been well characterized. However, FDA considers that the interpretation of dose proportionality for the tablet formulation is limited by the available data as only 200 mg and 400 mg BID dose levels were tested in the study. In addition, only 400 mg tablets BID were evaluated in the efficacy and safety studies (Study X2101 and Study A2201), thus a power model could not be used to test the dose proportionality. The dose-normalized Cmax and AUC_{inf} following single dose of 200 mg to 600 mg capmatinib tablets in healthy subjects were visually comparable across the dose range of 200 mg to 600 mg (Figure 6). Overall, capmatinib exposure increased with tablet dose levels in an approximately dose proportional manner over a single dose range of 200 to 600 mg, which may be extrapolated to QD and BID dosing given capmatinib has time-independent PK.

Figure 6 Boxplot of Dose-Normalized AUC_{inf} and C_{max} of Single Dose Capmatinib Tablets in Healthy Subjects



Note: (1) Diamonds represent the mean and circles represent values outside of 1.5*IQR.
(2) Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.

(Data source: Figure 3-1a on Page 105 to 106 in the Summary of Clinical Pharmacology)

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data and The Applicant's Position:

Yes.

The dose of 400 mg bid for capmatinib tablets provided robust efficacy in subjects with MET mutated NSCLC, especially in the first line setting, where a 67.9% ORR was achieved and a 40.6% ORR was achieved in the pretreated setting. In the context of these robust findings, capmatinib demonstrated a wide therapeutic margin, as evidenced by relatively flat exposure–response relationships with respect to efficacy endpoints BOR, DOR, or tumor size change from baseline in Cohort 4 or Cohort 5b. The relationship was inconclusive for exposure-PFS although

there was a positive trend. In addition, 400 mg b.i.d. was expected to be sufficient to maintain constant target inhibition as 96% (90% CI: 94%, 98%) of patients have steady state capmatinib plasma concentration above IC95 (132 ng/mL) for MET inhibition during the dosing interval

The FDA's Assessment:

FDA agrees with the Applicant's position that clinical data in Study A2201 provided efficacy data to support the approval of capmatinib tablets at 400 mg BID in patients with MET mutated NSCLC. The relatively flat exposure-efficacy relationship in Cohort 4 and Cohort 5b and the PK/PD model prediction of steady state trough capmatinib concentration in 96% of patients following 400 mg BID could reach IC_{95} for MET inhibition (Table 16) also support the 400 mg BID dosing regimen. However, FDA considers that the exposure-efficacy relationship is inconclusive given the limited sample size. See Pharmacometrics review for details.

Table 16 Proportion of Patients with $C_{trough,ss}$ > IC90 or IC95 for MET Inhibition

dose	IC90n	IC95n	n	IC90prop	IC90prop.lb	IC90prop.ub	IC95prop	IC95prop.lb	IC95prop.ub
200	305	254	310	0.9839	0.9721	0.9956	0.8194	0.7834	0.8553
300	308	288	310	0.9935	0.9861	1	0.929	0.905	0.953
400	309	297	310	0.9968	0.9915	1	0.9581	0.9393	0.9768

(Data source: Figure 5-25 on page 59 in the Report of population PK modeling)

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data and The Applicant's Position:

Yes. The proposed dose of 400 mg b.i.d. is effective and generally well tolerated for the patient population for which the indication is being sought. More details on dosing is provided in Section 6.2.2. The proposed 400 mg b.i.d. dose regimen provided robust efficacy in the targeted population, and ensured that the majority of patients (> 96%) could achieve sustained MET inhibition during the dosing interval. While no clear association between exposure and efficacy was observed, the trend of longer PFS with higher exposure shown in one of the exposure-efficacy analyses (the extended cox regression analysis suggested a trend towards a better treatment PFS benefit with higher capmatinib exposure in Cohort 4) supports the clinical benefit provided by this 400 mg b.i.d. dose. With regard to safety, the proposed 400 mg b.i.d. dosage regimen for capmatinib combined with proper dose modifications resulted in an acceptable safety profile and effective AE management of the emerging safety events.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that dosing regimen of capmatinib 400 mg BID is appropriate for the general patient population for which the indication is being sought.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data and The Applicant's Position:

No. No alternative dosing regimen is required for subpopulations based on intrinsic patient factors. Details are provided in Section 6.2.2.2

The FDA's Assessment:

FDA generally agrees with the Applicant's position that no alternative dosing regimen is required for subpopulations based on intrinsic patient factors. See details in Section 6.2.2.2.

MET GCN amplification and response: MET exon 14 skipping mutations and MET amplification overlap in a subset of patients with NSCLC. FDA explored the effects of MET amplification on treatment response in cohorts 4 and 5b of Study CINC280A2201 (MET exon 14 skipping mutation-positive irrespective of MET amplification, expressed as gene copy number (GCN)). The presence of MET GCN amplification was assessed by fluorescence in situ hybridization (FISH) in fresh or archival tumor samples. Approximately 88% of patients enrolled in cohorts 4 and 77% of patients enrolled in cohort 5b had MET GCN amplification results available (N=82).

Three different thresholds (amplified defined as GCN ≥4, GCN ≥6, or GCN ≥10) were applied for this analysis. Using these thresholds, there were 60 (GCN ≥4), 35 (GCN ≥6), and 15 (GCN ≥10) patients with tumors positive for MET amplification in cohorts 4 and 5b combined. MET GCN values ranged from 2-30 (Median=6) in cohort 4 and from 2-16 (Median=5) in cohort 5b. Overall response rates (PR+CR) for amplified versus non-amplified subgroups were 57% vs. 18% for GCN ≥4, 57% vs. 38% for GCN ≥6, and 60% vs. 43% for GCN ≥10. These differences appeared to be mainly driven by the results of cohort 4.

Exploratory subgroup analyses of BIRC-assessed response by MET GCN amplification suggest higher response rates in patients with co-occurring MET exon 14 skipping mutations and MET GCN amplification. Results should be interpreted with caution due to small numbers and lack of a consensus definition for amplification. More data are required to assess whether MET amplification could be useful as a potential complementary biomarker to help guide treatment with capmatinib. The applicant should continue to evaluate the effects of MET GCN on response in ongoing or planned trials.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food effect:

Data:

- Study X2107 (in healthy subjects) evaluated the effect of food (low-fat and high-fat meals) on the PK of capmatinib, following single oral administration of 600 mg film coated tablet (FCT). A high-fat meal increased the bioavailability of capmatinib (AUCinf by 46%) without a clinically relevant impact on the rate of absorption (Cmax increase by 15%) compared to fasted conditions. A low-fat meal had no clinically relevant impact on the rate or extent (AUCinf increase by 20%, Cmax increase by 11%) of capmatinib absorption.
- Study A2108 (in subjects with solid tumors) further evaluated the PK and safety of capmatinib when administered with food at doses of 300 mg and 400 mg b.i.d. using the FCT. The capmatinib tablet was given with unrestricted type of meals except on the morning of PK collection days where a high-fat meal was required. At 400 mg b.i.d., geometric mean AUC following a single dose (AUC0-12h) or at steady‑state (AUC0-12h,ss) was 13% and 17% lower, respectively, compared to the corresponding AUC observed in Study A2201 where capmatinib was given under fasted conditions (at least 1 h before or 2 h after a meal). Geometric mean Cmax following single dose (Cmax) or at steady state (Cmax_ss) was 28% and 36% lower, respectively, compared to those in Study A2201. A delayed Tmax (median Tmax 4 h) was observed compared to the Tmax achieved under fasted conditions (median Tmax 1 hr). The overall variability in exposure was lower when capmatinib was given with food. Capmatinib was well tolerated at both dose levels with no dose-limiting toxicity (DLT) observed. Overall, the safety profile for capmatinib in Study A2108 was similar compared to that in Study A2201.
- To avoid confounding effect due to PPI use on the exposure comparison between fasted [Study A2201] and fed condition [Study A2108], the exposure data was further stratified based on PPI usage during PK evaluation. For those who did not use PPI, geometric mean AUC values were comparable between Studies A2201 and A2108, while geo-mean Cmax was slightly lower in Study A2108 following a single dose (15%) and at steady state (24%) compared to Study A2201, which further confirmed the lack of food effect in patients.
-

The Applicant's Position:

While a modest positive food effect was observed in healthy subjects in the high-fat meal arm receiving a single dose of capmatinib, there was no clinically significant difference in exposure when capmatinib was given under fasted conditions or with food in subjects with cancer following single dose or dosed on a continuous schedule. In addition, the likelihood of the targeted patient population taking high fat, high calorie meals regularly is low. Given the above, together with the safety data, it is recommended that capmatinib may be administered with or without food, as food does not alter capmatinib bioavailability to a clinically meaningful extent.

The FDA's Assessment:
FDA generally agrees with the Applicant's position that a high fat meal had a modest positive effect on capmatinib exposure while a low-fat meal had no clinical meaningful effect based on the results from the dedicated food effect study X2107 in healthy subjects. However, FDA does not agree with the Applicant's (b) (4)

FDA generally agrees with the Applicant's recommendation that capmatinib may be taken with or without food given a low-fat meal had no clinical meaningful effect on capmatinib exposure and capmatinib was tolerable at 400 mg BID with no dose-limiting toxicity (DLT) observed during the first 28 days of therapy in Study A2108. In addition, the safety profile for capmatinib in Study A2108 in which capmatinib was taken with food was similar compared to that in Study A2201 in which capmatinib was administered in the fasted condition.

In addition, comparing the safety profiles between Cohort 6 and Cohorts 1-5 in Study A2201, where capmatinib was given irrespective of food in Cohort 6 and under fasting conditions in Cohorts 1-5, FDA found the safety profile in Cohort 6 did not deviate from that in Cohort 1-5, indicating the food intake did not have a clinical meaningful impact on capmatinib safety. The safety analysis included (1) most frequent AEs suspected to be study drug related in ≥ 20% of all patients [peripheral edema (42%) and Nausea (33%)] , (2) Grades 3/4 AEs (> 5%) suspected to be study drug related [peripheral edema (8%), lipase increased (5%), and ALT increased (5%)], (3) AEs leading to study drug permanent discontinuation reported in ≥ 1% patients [peripheral edema (1.8%), pneumonitis (1.8%), and fatigue (1.5%)], and (4) most frequent AEs requiring dose adjustment and/or interruption in ≥ 5% of all patients [peripheral edema (12%), creatinine increased (8%), nausea (7%) and vomiting (7%)] (Table 17-Table 20).

Table 17 Most Frequent AEs (%) Suspected to be Study Drug Related in Cohorts 1-6

All Grades (≥ 20%)	Cohort 1a (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=27)**
Peripheral Edema (42%)	38	33	35	30	45	60	68	**44**
Nausea (33%)	36	29	30	30	36	40	39	**26**

Table 18 Grades 3/4 AEs (%) Suspected to be Study Drug Related in Cohorts 1-6

Grades 3/4 (≥ 5%)	Cohort 1a (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=27)**
Peripheral Edema (8%)	7	5	4	3	15	13	7	**4**
Lipase Increased (5%)	3	7	2	7	9	0	7	**4**
ALT Increased (5%)	7	2	4	0	7	7	7	**0**

Table 19 AEs (%) Leading to Study Drug Permanent Discontinuation in Cohorts 1-6

All Grades (≥ 1%)	Cohort 1a (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=27)**
Peripheral Edema (1.8%)	1.4	2.4	3.7	0	1.4	0	3.6	**0**
Pneumonitis (1.8%)	2.9	0	0	3.3	4.3	0	0	**0**
Fatigue (1.5%)	0	0	1.9	6.7	1.4	6.7	0	**0**

Table 20 Most Frequent AEs (%) Requiring Dose Adjustment and/or Interruption in Cohorts 1-6

All Grades (≥ 5%)	Cohort 1a (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=27)**
Peripheral Edema (12%)	1	2	4	0	1	0	4	**0**
Creatinine Increased (8%)	9	2	7	10	13	0	18	**0**
Nausea (7%)	7	12	2	7	12	0	4	**4**
Vomiting (7%)	7	5	7	10	7	7	4	**4**

Effect of concomitant medication on capmatinib:
Data:

Strong CYP3A4 inhibitors: In healthy subjects, co-administration of a single 200-mg capmatinib dose with a strong CYP3A4 inhibitor, itraconazole (200 mg q.d. for 10 days), increased capmatinib AUCinf by 42% with no increase in capmatinib Cmax compared to administration of capmatinib alone.
CYP3A4 inducers: In healthy subjects, co-administration of a single 400-mg capmatinib dose with the strong CYP3A4 inducer rifampicin (600 mg q.d. for 9 days) decreased capmatinib AUCinf by 67% and Cmax by 56% compared to administration of capmatinib alone. Physiologically based pharmacokinetic (PBPK) modeling predicted a weak effect of a 44% reduction in capmatinib AUC0-12h and 34% reduction in Cmax at steady state when administered concomitantly with the moderate CYP3A4 inducer, efavirenz (600 mg q.d. for 20 days).
Gastric pH-altering agents: In healthy subjects, co-administration of a single 600-mg capmatinib dose with the PPI rabeprazole (20 mg q.d. for 4 days) decreased capmatinib AUCinf by 25.2% and Cmax by 37.5%. A subgroup analysis was conducted to compare the PK of PPI user with non PPI user in patients in study A2108. The results was to be considered similar to what was observed in healthy subject study within the limitation of the small sample size and parallel group comparison.

The Applicant's position:

Based on the results presented above, it is recommended to avoid the concomitant use of capmatinib with strong CYP3A inducers. (b) (4)

(b) (4)

The FDA's Assessment:
FDA agrees with the Applicant's position regarding the labeling recommendation of the concomitant use of capmatinib with strong CYP3A inducers. However, FDA does not agree with the Applicant's position regarding the (b) (4)

Strong CYP3A4 inhibitors
FDA does not agree with the Applicant's proposed labeling language of (b) (4)

, (b) (4)

(b) (4). FDA recommends that closely monitor patients for toxicities during concomitant use of TABRECTA with strong CYP3A inhibitors. This recommendation is based on the following additional data provided by the Applicant at FDA's request:

a. No clinically significant safety difference in who used concomitant medications of strong, moderate or weak CYP3A inhibitors with regards to treatment related AEs, the worst post-baseline hematology and chemistry lab, and AEs requiring dose adjustment, interruption, or permanent discontinuation of capmatinib.

b. No new safety signals identified upon medical review of patient profiles who used concomitant medications of strong, moderate or weak CYP3A inhibitors. Of note, the sample size is small (n=8) for patients who took strong CYP3A inhibitors.

FDA agrees with the Applicant's position that in general, there was no clinically significant safety difference in patients used concomitant medications of strong, moderate or weak CYP3A inhibitors. However, FDA notices a trend that the percentage of patients with treatment related peripheral edema lead to dose adjustment or interruption was higher when used concomitant medications of strong CYP3A inhibitors (< 25% of capmatinib treatment duration) comparing to those without using CYP3A inhibitors (Table 21). The same trend is seen for either all grades or Grade 3/4 edema in Study A2201 or for all NSCLC patients (data not shown). FDA acknowledges the data limitation due to small sample size of patients taken strong CYP3A inhibitors.

Table 21 Edema Requiring Dose Adjustment or Interruption by Subgroups of CYP3A4 Inhibitors in Study A2201

	Non-CYP3A4 Inhibitors (N=185)	Weak CYP3A4 Inhibitors (N=101)	Moderate CYP3A4 Inhibitors (N=1)	Strong CYP3A4 Inhibitors (N=2)	Other-Weak CYP3A4 Inhibitors (N=28)	Other-Moderate CYP3A4 Inhibitors (N=11)	Other-Strong CYP3A4 Inhibitors (N=6)
All Grades Peripheral Edema							
Number of patients requiring dose adjustment (%)	8 (4)	7 (7)	0	0	6 (21)	1 (9)	2 (33)
Number of patients requiring dose Interruption (%)	12 (7)	8 (8)	0	1 (50)	2 (7)	2 (18)	4 (67)
Grades 3/4 Peripheral Edema							
Number of patients requiring dose adjustment (%)	2 (1)	2 (2)	0	0	2 (7)	1 (9)	1 (17)
Number of patients requiring dose Interruption (%)	4 (2)	5 (5)	0	0	2 (7)	2 (18)	2 (33)

Note:
(1) Weak/Moderate/Strong CYP3A4: Patients who took concomitant medications, known to be a weak/moderate/strong CYP3A4 inhibitors, for >=25% of INC280 treatment duration, respectively and separately.
(2) Other-Weak/ Other-Moderate/ Other-Strong CYP3A4: Patients who took concomitant medications, known to be a CYP3A4 inhibitors, for < 25% of INC280 treatment duration or with missing start/end dates of the medication for respective category.

Strong/Moderate CYP3A4 inducers

FDA agrees with the Applicant's proposed labeling recommendation that concomitant use of capmatinib with strong CYP3A inducers should be avoided given that the AUC_{inf} of capmatinib was decreased by 67% when used with rifampicin which may decrease capmatinib efficacy. Regarding coadministration of capmatinib with a moderate CYP3A inducer, physiologically based pharmacokinetic (PBPK) simulations predicted a 46% reduction in capmatinib $AUC_{0\text{-}12h}$ and 35% reduction in C_{max} at steady state when capmatinib is administered concomitantly with efavirenz (a moderate CYP3A inducer), which may decrease capmatinib efficacy (see PBPK review in the OCP appendices). Given no available clinical data to assess the potential loss of capmatinib efficacy when coadministering of capmatinib with moderate CYP3A inducers as no patients took a strong or moderate CYP3A inhibitors in Study A2201, FDA recommends that concomitant use of moderate CYP3A inducers with TABRECTA be avoided.

(b) (4)

FDA recommends removal of the Applicant's proposed labeling paragraph under Section 7 Drug Interactions regarding (b) (4)

Effect of capmatinib on concomitant medication:
Data:

Substrates of CYP enzymes (CYP1A2, CYP3A4, and CYP2C): In subjects with cancer, co-administration of caffeine (a sensitive CYP1A2 substrate) with multiple doses of capmatinib (400 mg b.i.d.) increased caffeine AUCinf by 134% with no increase in Cmax compared to administration of caffeine alone. In subjects with cancer, co-administration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of capmatinib (400 mg b.i.d.) did not cause any clinically significant increase in midazolam exposure compared to administration of midazolam alone.

Capmatinib showed reversible inhibition potential for CYP2C8, CYP2C9 and CYP2C19 in HLM in vitro. Capmatinib also showed weak induction of CYP2C9 in cultured human hepatocytes. A verified Simcyp PBPK model and CYP‑probe substrate compound files in Simcyp library (Repaglinide, Warfarin and Omeprazole) were used to simulate the effect of capmatinib on CYP2C8, CYP2C9, CYP2C19. No significant exposure change was predicted for warfarin and omeprazole. Capmatinib was predicted to be a weak CYP2C8 inhibitor with a modest 23% increase in Cmax and 39% increase in AUCinf of repaglinide when co-administrated with capmatinib at 400 mg b.i.d.

Substrates of transporters (P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)): In subjects with cancer, co-administration of digoxin (a P-gp substrate) with multiple doses of capmatinib (400 mg b.i.d.) increased digoxin AUCinf by 47% and Cmax by 74% compared to administration of digoxin alone. Also in subjects with cancer, co-administration of rosuvastatin (a BCRP substrate) with multiple doses of capmatinib (400 mg b.i.d.) increased rosuvastatin AUCinf by 108% and Cmax by 204% compared to administration of rosuvastatin alone.

Effect on renal transporters (MATE1 and MATE 2K): Capmatinib showed potent inhibition of renal transporter MATE1 and MATE2K with Ki of 0.28 and 0.29 µM, respectively, in vitro. A

inhibition risk was indicated by Cmax,ss/Ki ratios of 1.66 and 1.60 in the static risk assessment using plasma capmatinib concentration. It was reported that a small fraction (10-40%) of the serum creatinine was cleared via active tubular secretion by these renal transporters such as MATE and OAT in addition to renal glomerular filtration. Another endogenous renal function biomarker, cystatin C, is solely cleared through glomerular filtration with no involvement of active transporters. In Study A2102, the time course (pre-dose, 2, 4, 8, 24, 48 and 72 h post-dose) of serum creatinine and cystatin C was investigated following single dose of capmatinib (200 mg for inhibition arm, 400 mg for induction arm). All subjects showed transient grade 1 serum creatinine increase post-dose while no change in cystatin C level was observed during the 72 h sampling period. 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.

The Applicant's Position:

Clinical DDI study results showed that capmatinib is not a CYP3A inhibitor, but a moderate CYP1A2 inhibitor. (b) (4)

PBPK model predicted capmatinib to be a weak CYP2C8 inhibitor. The only known CYP2C8 substrate with narrow therapeutic index is paclitaxel, which is unlikely to be given concomitantly with capmatinib. Therefore, the weak DDI between capmatinib and sensitive CYP2C8 substrate is not considered clinically relevant.
Clinical DDI study results showed that capmatinib is an inhibitor of P-gp and BCRP. It is therefore recommended to exercise caution during concomitant use of capmatinib with P-gp and BCRP substrates.
Based on the in vitro data, static DDI assessment and renal biomarker data, capmatinib may inhibit MATE1 and MATE2K at clinically relevant concentrations.

The FDA's Assessment:
FDA does not agree with the Applicant's position regarding the (b) (4) FDA agrees with the Applicant's assessment of the clinical impact of capmatinib on sensitive CYP2C8 substrates.

FDA does not agree with the Applicant's proposed labeling recommendation of (b) (4) FDA recommends if coadministration is unavoidable with CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information because caffeine AUC_{inf} was increased by 134% when it was coadministered with capmatinib.

Similarly, FDA does not agree with the Applicant's proposed labeling recommendation of [redacted] (b) (4) (b) (4) . FDA recommends if coadministration is unavoidable with P-gp orBCRP substrates where minimal concentration changes may lead to serious adverse reactions, decrease the dosage of P-gp or BCRP substrates in accordance with the approved prescribing information. This recommendation is supported by that digoxin (P-gP substrate) AUC_{inf} was increased by 47% and C_{max} by 74% and rosuvastatin (BCRP substrate) AUC_{inf} was increased by 108% and C_{max} by 204% when they coadministered, respectively with capmatinib.

FDA agrees with the Applicant's position that the impact of capmatinib on sensitive CYP2C8 substrates is not expected to be clinically relevant as capmatinib is a weak CYP2C8 inhibitor. See PBPK review regarding the validation of the Simcyp PBPK model used to simulate the effect of capmatinib on CYP2C8, CYP2C9, CYP2C19. The simulations predicted no significant exposure change for warfarin and omeprazole which need to be validated.

FDA agrees with the Applicant's position that capmatinib may inhibit substrates of MATE1 and MATE2K at clinically relevant concentrations based on the in vitro data, static DDI assessment and renal biomarker data. At FDA's request the Applicant addressed this high inhibition risk by proposing appropriate labeling language to minimize the risk for concomitant use of MATE1 and MATE2-K substrates such as dofetilide for which a minimal exposure increase may result in serious adverse reactions. A subsection of MATE1 and MATE2K substrates was added under section 7.2 Effect of TABRECTA on Other Drugs. FDA recommends if coadministration is unavoidable with MATE1 or MATE2K substrates where minimal concentration changes may lead to serious adverse reactions, decrease the dosage of MATE1 and MATE2K substrates in accordance with the approved prescribing information.

6.3.2.5 Are the PK assays for capmatinib adequate?

FDA evaluated the Applicant's bioanalytical methods for capmatinib PK assessments. The results are summarized in Table 22. See the details in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods from Pages 30 to 69 and Applicant's response to clinical pharmacology information request (IR) dated 1/10/2020 (SN0005) in EDR submission of NDA 213591.

Table 22 Evaluation Summary on the Applicant's Bioanalytical Methods

Bioanalytical Study Number	Test Site	In Study Method Performance	Method Validation	Cross Validation
DMPK R1100266A (capmatinib)	(b) (4)	Studies A2101, X1101, X2102, X2103,	Acceptable	NA
DMPK R140090 (capmatinib)		Study A2108,	Acceptable	Acceptable (DMPK R140090 vs. DMPK R1100266A)
DMPK R1400617 (capmatinib and its metabolite CMN288)		Studies A2101, A2102, A2103, A2105, A2106, A2201, X1101, X2102, X2106, X2107,	Acceptable	Acceptable (DMPK R1400617 vs. DMPK R1100266A)
DMPK R1701049 (capmatinib and its metabolite CMN288)		Studies A2102, A2108, A2109, A2201,	Acceptable	Acceptable (DMPK R1701049 vs. DMPK R1400617)

In summary, the assays used for capmatinib concentration measurement are appropriately validated and adequate for capmatinib PK assessments.

Primary Reviewers	Team Leaders
Runyan Jin, Ph.D.	Hong Zhao, Ph.D.
Youwei Bi, Ph.D.	Jiang Liu, Ph.D.
Manuela Grimstein, Ph.D.	Yuching Yang, Ph.D.
Jeffrey Kraft, Ph.D.	Rosane Charlab Orbach, Ph.D.

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

All studies pertinent to the evaluation of safety and efficacy are summarized in Table 23.

Table 23: Listing of Clinical Trials Relevant to this NDA

Trial identity /Status	NCT no.	Trial design	Regimen / schedule/ route	Study endpoints	Treatment duration/ follow up	No. of subjects enrolled	Study population	No. of centers and countries
Studies to support efficacy and safety								
A2201 Ongoing	NCT02414139	Phase II, multicenter, open-label study	400 mg b.i.d. tablet	**Primary**: ORR per BIRC **Key secondary:** DOR per BIRC **Other secondary**: ORR and DOR per Investigator; TTR, DCR, and PFS per Investigator, and BIRC; OS; and safety	Median exposure: Cohort 4 = 22.1 weeks Cohort 5b = 47.9 weeks	334 Cohort 4 = 69 Cohort 5b = 28	Adults with EGFRwt[1], ALK-negative rearrange-ment, advanced or metastatic (stage IIIB or IV) NSCLC[2]	152 centers across 25 countries
X2102 Completed	NCT01324479	Phase I, open-label dose escalation, with expansion study	Dose escalation: 100, 200, 250, 350, 450 mg b.i.d. capsule; 400, 600 mg b.i.d.	**Primary[3]:** MTD **Secondary[3]:** BOR, safety and tolerability, c-MET signaling inhibitory activity by IHC, and PK **Key**	Median exposure = 8 weeks	131 Dose escalation = 38 Dose expansion = 93	Adults with c-MET dependent advanced solid tumors	33 centers across 14 countries

			tablet Dose expansion: 400 mg b.i.d. - tablet	**secondary[4]:** ORR at MTD/RP2D **Other secondary[4]**: safety and tolerability; PFS, DOR, and DCR; and PK				
Studies to support safety								
X2101T Completed	NCT01072266	Phase I, open-label, dose-escalation study	10, 20, 50, 70, 150, 200, 300, 400 mg q.d. capsule; 50, 200, 300 mg b.i.d. - capsule	**Primary:** DLT and MTD **Secondary:** highest level of phospho c met inhibition in blood and tumor biopsies; PK; BOR	Median exposure = 8 weeks	45	Adult subjects with advanced malignancies	2 centers in the USA
X1101 Completed	NCT01546428	Phase I open-label, multicenter dose escalation with an expansion part	100, 200, 400, 500, 600, 800 mg q.d. - capsule; 400, 600 mg b.i.d. capsule; 200, 400 mg b.i.d. tablet	**Primary:** determine MTD **Secondary**: safety and tolerability; BOR; PK	Median exposure = 7 weeks	44	Japanese subjects with advanced solid tumors	2 centers in Japan
A2103 Completed	NCT02520752	Phase I, multicenter, open-label, single-sequence drug-drug interaction study	400 mg b.i.d. - tablet	**Primary:** effect of multiple doses on PK of single dose of midazolam and caffeine **Key**	Median exposure = 7.43 weeks	37	Subjects with cMET dysregulated advanced solid tumors	8 centers across 5 countries

				secondary: safety and tolerability **Other secondary**: ORR, DCR				
A2105 Completed	NCT02623623	Phase I, multicenter, open-label, single-sequence drug-drug interaction study	400 mg b.i.d. - tablet	**Primary:** effect of multiple doses on PK of single dose of digoxin and rosuvastatin **Secondary**: safety and tolerability; PK	Median exposure = 7.14 weeks	32	Subjects with cMET dysregulated advanced solid tumors	8 centers across 5 countries
A2108 Completed	NCT02925104	Phase I, multicenter, open label, dose escalation study (with food)	Dose escalation: 300, 400 mg b.i.d. tablet; Expansion phase: 400 mg b.i.d. - tablet	**Primary:** DLT, PK **Secondary**: safety	Median exposure = 11.8 weeks	35	Subjects with cMET dysregulated advanced solid tumors	12 centers across 8 countries
Other studies (clinical pharmacology)								
X2103 Completed	Not applicable	Randomized, open-label, two-sequence, two-period, crossover study	600 mg single dose tablet and capsule	**Primary:** relative bioavailability of film-coated tablets to hard gelatin capsules **Secondary**: safety and tolerability	Single dose	24	Healthy volunteers	Single center in Germany
X2106 Completed	Not applicable	Open-label ADME study	600 mg single dose capsule	**Primary:** rates and routes of excretion of [^{14}C]-related radioactivity	Single dose	6	Healthy volunteers	Single center in the Netherlands

				, in urine and feces; PK of total radioactivity in blood and plasma; PK **Secondary**: safety and tolerability				
X2107 Completed	Not applicable	Randomized, single-center, open-label, three-period, six-sequence, crossover study (food effect)	600 mg single dose tablet	**Primary:** effect of food on rate and extent of exposure **Secondary**: effect of food on safety and tolerability	Single dose (in each of 3 treatment periods)	24	Healthy volunteers	Single center in Germany
A2101 Completed	Not applicable	Single-center, open-label, two-period, single-sequence study	600 mg single dose tablet	**Primary**: effect of multiple doses of rabeprazole on PK **Secondary:** safety and tolerability	Single dose (in each of 3 dosing periods)	20	Healthy volunteers	Single center in Germany
A2102 Completed	Not applicable	Phase I, open label, two arm drug-drug interaction study	200, 400 mg single dose tablet	**Primary**: effect of itraconazole and rifampicin on single dose PK **Secondary:** safety and tolerability	Single dose (in each of 2 periods)	53	Healthy volunteers	Single center in Germany
A2106 Completed	NCT02474537	Open label, single-dose, multicenter, parallel-group, two-staged study	200 mg single dose tablet	**Primary:** PK in subjects with impaired hepatic function vs. normal hepatic function **Secondary**:	Single dose	31 Healthy volunteers = 10 Hepatic impaired subject	Healthy volunteers and subjects with hepatic impairment	4 centers in the USA

				safety and tolerability		s = 21		
A2109 Completed	Not applicable	Phase I, randomized, open-label, three-period, six-sequence crossover study		**Primary:** bioequivalence **Secondary:** safety and tolerability.	Single dose	78	Healthy volunteers	Single center in Germany

-BIRC: Blinded Independent Review Committee, ORR: Overall response rate, DOR: Duration of response, TTR: Time to response, DCR: Disease control rate, OS: Overall survival
[1] For exon 19 deletions and exon 21 L858R substitution mutations
[2] Who had failed 1-2 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
[3] For dose escalation and original expansion group
[4] For expansion group

The FDA's Assessment:

FDA agrees with Novartis' list of clinical trials relevant to this NDA.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy of capmatinib in patients with MET mutated locally advanced or metastatic NSCLC is generated primarily from Study A2201, the Phase II pivotal trial. This is a multicenter, single-agent, non-randomized study in adult patients with EGFRwt, advanced NSCLC.
Efficacy analyses are based on data from the 97 subjects with MET-mutated advanced/metastatic NSCLC enrolled in Cohort 4 (2L/3L: 69 subjects) and in Cohort 5b (1L: 28 subjects) who had completed at least 6 treatment cycles or had discontinued treatment earlier.
Supportive data are provided from Study X2102 (a Phase I, open-label dose-escalation study designed to assess the safety and tolerability of capmatinib in adult patients with MET dependent advanced solid tumors). Study X2102 provided the first evidence of efficacy of capmatinib in MET dysregulated (and specifically in MET mutated) NSCLC.

The clinical package also includes a Real-World Evidence (RWE) global retrospective chart collection (Study X2401) to describe the natural history of advanced MET dysregulated NSCLC. The analysis of the MET mutated NSCLC charts demonstrate that MET mutation is a negative prognostic factor and a predictor of limited response to standard therapies.

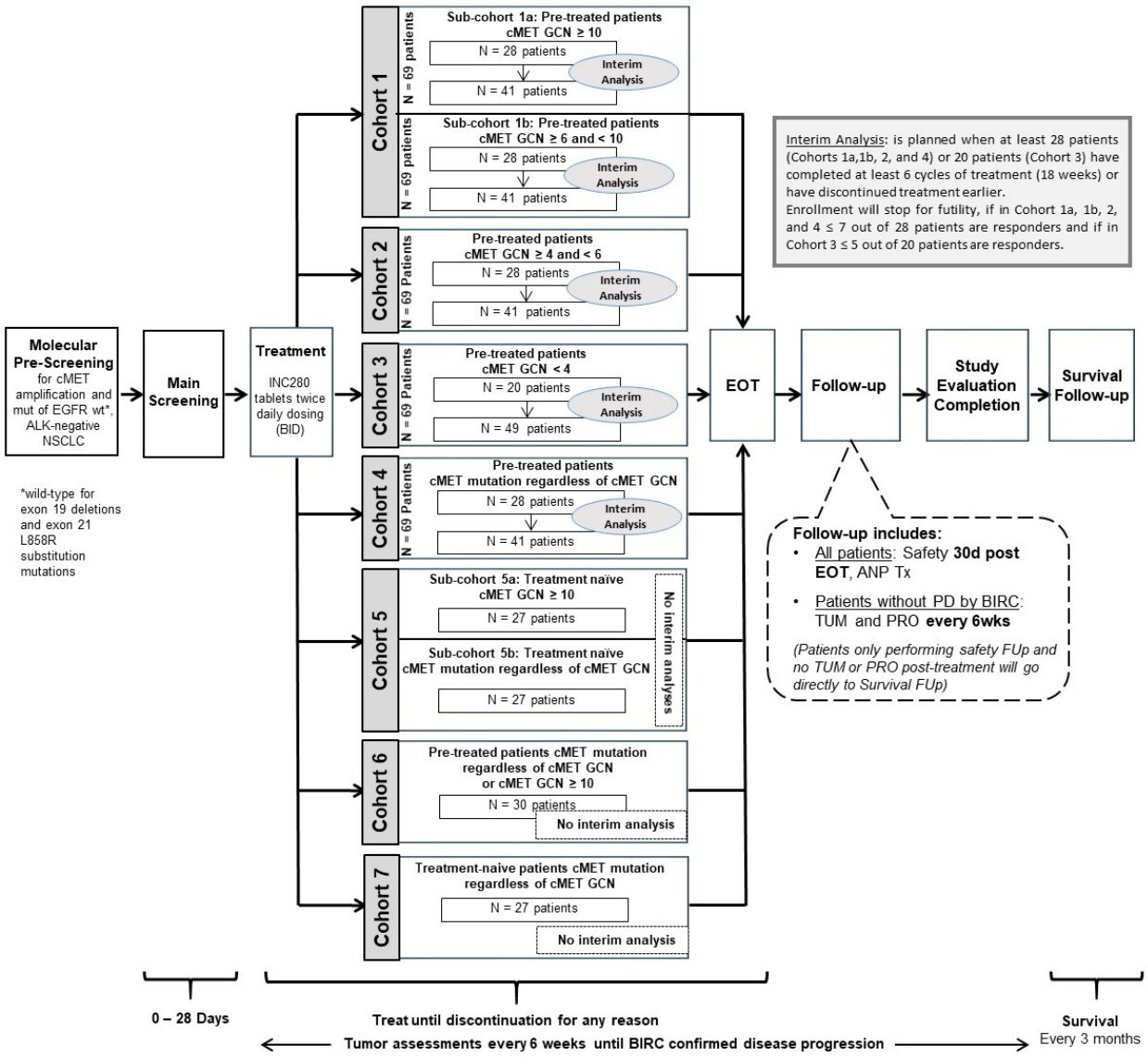
8.1.1. Study CINC280A2201

Trial Design

The Applicant's Description:

The study design of the pivotal study CINC280A2201 (referred to as Study A2201 here after) is presented in Figure 7.
The cohorts 4 and 5b are the basis for the efficacy data of capmatinib in MET mutated NSCLC in this NDA submission. All the remaining cohorts are primarily used to describe capmatinib safety.

Figure 7: Study design- Study CINC280A2201



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

Trial location: 152 sites across 25 countries in North and Latin America, Europe, and Asia enrolled a total of 334 subjects (69 subjects in Cohort 4 and 28 subjects in Cohort 5b).

Choice of control group: Not applicable as this was an non-randomized study.

Diagnostic criteria: 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 and c) MET mutation and/or amplification status as determined by:

Cohort	MET amplification (GCN)	MET mutation status
Prior treatment status: pretreated (2nd/3rd line)		
Cohort 1a	≥ 10	Negative
Cohort 1b	≥ 6 and < 10	Negative
Cohort 2	≥ 4 and < 6	Negative
Cohort 3	< 4	Negative
Cohort 4	Any GCN	Positive
Prior treatment status: pretreated (2nd line only)		
Cohort 6	≥ 10	Negative
Cohort 6	Any GCN	Positive
Prior treatment status: treatment-naive (1st line)		
Cohort 5a	≥ 10	Negative
Cohort 5b	Any GCN	Positive
Cohort 7	Any GCN	Positive

GCN=Gene copy number

Key inclusion and exclusion criteria: Subjects with histologically or cytologically confirmed diagnosis of Stage IIIB or IV NSCLC, with at least one measurable lesion as defined by RECIST 1.1, were enrolled in the study.
Cohorts 4 and 5b enrolled patients with MET exon 14 mutations (pretreated and treatment naive, respectively).

Other cohorts were: a) MET amplified patients who had failed one or two prior lines of therapy (in Cohorts 1a, 1b, 2, 3) b) MET amplified (GCN >10) or MET mutated patients with one prior therapy (Cohort 6), c) MET amplified with no prior systemic therapy for advanced disease (Cohort 5a), and d)MET mutated patients with no prior systemic therapy for advanced disease (Cohort 7).

Subjects with characterized EGFR mutations that predict sensitivity to EGFR therapy, ALK-positive rearrangement and presence or a history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years (excluding completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type) were excluded from the study.

Dose selection: Selection of the 400 mg b.i.d. dosing schedule for the capmatinib tablet formulation was based on the results from Study X2102. Details are provided in Section 6.2.2.1.

Study treatments, treatment assignment: The assignment of a subject to a particular cohort was coordinated by Novartis via IRT based on MET mutation and MET GCN pre-screening

results and prior treatment status. Capmatinib 400 mg b.i.d. was administered orally on a continuous twice daily dosing schedule.

Dose modification, dose discontinuation: A maximum of 2 dose reductions (to 300 mg b.i.d. and to 200 mg b.i.d.) was allowed after which the subject discontinued study treatment. Dose re-escalation of capmatinib to the previous dose level was allowed only once, and if no AE leading to dose modification was observed after at least 1 cycle (3 weeks) of study treatment at the reduced dose.

Administrative structure: Trial oversight was managed by a Study Steering Committee (SCC). SCC consisted of Investigators and sponsor representatives with experience and expertise in leading the conduct of clinical studies within this disease area. SCC was responsible for trial conduct with highest scientific and ethical standards.

Procedures and schedule: Imaging assessments were performed at screening/baseline (Day -28 to Day - 1 prior to Cycle 1 Day 1) and every 6 weeks starting from Day 1 of Cycle 1. Vital signs, and hematological and biochemical laboratory tests were performed at Day 1 and Day 15 of Cycle 1 and then at Day 1 of subsequent cycles. Adverse events were recorded continuously until 30 days after the last dose of study treatment. ECG assessments were performed at Day 1 and Day 15 of Cycle 1, Day 1 of Cycle 3 and at End of study treatment visit.

Concurrent medications: All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose administration of capmatinib through 30 days after the last dose of capmatinib were recorded in the Concomitant Medications or Surgical and Medical Procedures eCRF, respectively. Medications included not only physician prescribed medications, but also all over-the-counter medications, herbal preparations, food supplements, and vitamins

Concomitant medication administered was representative of that routinely prescribed for subjects with locally advanced or metastatic NSCLC and/or for other illnesses commonly encountered in populations of a similar age. These subjects typically have multiple medical problems requiring ongoing treatment.

Treatment compliance: No formal measurements of study treatment concentrations were performed for the purpose of establishing compliance with treatment. The Investigator and/or study personnel assessed subject compliance with capmatinib at each visit to the clinic. In addition, capmatinib was detected in all of the plasma samples obtained for PK analysis, indicating that the subjects were exposed to the study drug.

Study Endpoints

The Applicant's Description: The primary evaluation of the antitumor activity of capmatinib was based on

- overall response rate (ORR) by BIRC assessment (primary endpoint) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, supplemented by DOR per BIRC (key secondary endpoint)

The other endpoints of the study were:

- TTR,
- DCR,
- PFS as assessed by BIRC and the Investigator,
- OS.

Other study endpoints included incidence of AEs, SAEs, change in vital signs, laboratory results, and ECG.

At an End-of-Phase II (EOP2) meeting on 01-Mar-2017, FDA agreed that the proposed study endpoints and statistical assumptions would be acceptable for submission if the ORR was large in magnitude and durable, and a description of the natural history of subjects with NSCLC harboring MET-mutations or MET amplification (RWE chart collection) was provided. The chosen endpoints were considered appropriate for a Phase II study, in a rare subject population with a high unmet need. Furthermore, the efficacy assessments performed in this study were standard for a NSCLC indication, and were therefore appropriate for the MET-mutated NSCLC subject population.

Acknowledging that non-randomized studies may be prone to assessment bias, BIRC assessment was employed to ensure independent assessment of response rate. BIRC review was based on double reader and adjudication to further ensure objectivity of the data review. The primary and key secondary endpoints (ORR and DOR, respectively) are assessed per BIRC. Other secondary efficacy endpoints including time-to-response (TTR), disease control rate (DCR), and PFS have also been assessed per BIRC.

The FDA's Assessment:
The study endpoints described above by Novartis are acceptable. The primary efficacy endpoint of the study is ORR per RECIST 1.1 as assessed by BIRC. The secondary endpoints include DOR, PFS and OS. Time-to-event endpoints (PFS and OS) are difficult to interpret in single arm trials without a control arm and are analyzed in a descriptive manner for this review.

Statistical Analysis Plan and Amendments

The Applicant's Description: The SAP was agreed upon and finalized prior to the conduct of efficacy analysis.

Efficacy analysis: The primary variable used to evaluate the antitumor activity of capmatinib was ORR, which was defined as the proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR), as assessed per RECIST 1.1 by BIRC. The primary analysis of ORR was performed on the full analysis set (FAS) which consisted of all subjects who received at least one dose of capmatinib. ORR was estimated by cohort and the exact 95% CI was provided.

Treatment with capmatinib was considered to have clinically relevant efficacy in the pretreated Cohort 4 if an ORR ≥ 35% was observed with a lower bound of exact 95% CI greater than 25%. In the treatment naïve Cohort 5b, treatment with capmatinib was considered to have clinically relevant efficacy if an ORR ≥ 55% was observed with a lower bound of exact 95% CI greater than 35%.

Key secondary endpoint (DOR by BIRC) and other secondary endpoint analyses were performed based on the FAS. DOR was calculated only for subjects with a confirmed response (CR or PR), DOR (by BIRC) and was defined as the time from first documented response (CR or PR) to the date of first documented PD or death due to any cause. If a subject did not have an event, DOR was censored at the date of last adequate tumor assessment.

Duration of response was described in tabular and graphical format using Kaplan-Meier (KM) methodology. If the primary analysis on ORR by BIRC assessment was considered positive, DOR by BIRC assessment was to be summarized by subgroup and assessed on PPS too. DOR by Investigator assessment was also analyzed. The distribution of other endpoints such as TTR, OS, and PFS were also estimated using KM methodology and medians along with, 95% CIs provided. Concordance/discordance of BOR between BIRC and Investigator assessments was tabulated by cohort.

The statistical plan was amended four times during the study to reflect changes in the protocol. The key changes included additional analyses on time to first occurrence of grade 3-4 AESI and durations, as well as time to first occurrence, of any grade AESI (including grade 3/4) were.

Safety analysis: All safety analyses were performed based on the Safety set (consisting of all subjects who received at least one dose of capmatinib) by cohort and also for all subjects. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. All AEs were coded using Medical Dictionary of Regulatory Activities (MedDRA), Version 22.0, to ensure consistency. All AE summaries were

presented (frequency counts and percentages) by system organ class and/or preferred term, and maximum grades, except where otherwise noted.

Laboratory data from all sources (central and local laboratories) were combined. Laboratory data were classified into CTC grades according to the NCI CTCAE v4.03. If CTCAE grading did not exist for some parameters, classification into low/normal/high groups by means of laboratory normal ranges was used.

PK analysis: PK data analyses were performed on the pharmacokinetic analysis set (PAS) which consisted of all subjects who received at least one planned dose of capmatinib and provided at least one evaluable PK concentration. PK data from all cohorts except Cohort 6 were reported. Cohort 6 was excluded as the food condition was different in this cohort, capmatinib being administered with or without food only in Cohort 6, but in the fasted state in all other Cohorts. Summary statistics were presented for concentrations of capmatinib and its metabolite CMN288 (M16) by study day and scheduled time point.

The FDA's Assessment:

FDA agrees with the applicant's description of primary and secondary endpoints and statistical analysis plan. FDA does not abide by the target ORR selected by the applicant for efficacy assessment but allows it only as a guide to facilitate sample size calculation. Time-to-event endpoints such PFS and OS are not interpretable and are considered descriptive in non-randomized open-label trials without a control arm. FDA reviewed the final versions of the protocol and SAP and found them to be acceptable. Four versions of SAPs mentioned in the description were not submitted with this application. The final SAP did not include a summary of changes from the previous versions.

Protocol Amendments

The Applicant's Description: The study protocol was amended 6 times. These amendments were not considered to have affected the interpretation of study results. The key features of each amendment are summarized in Table 24.

Table 24: Key Aspects of Protocol amendments

Amendment number/Date/ No of subjects enrolled at the time of amendment	Key protocol changes	Main rationale for amendment
Amendment 1/ 27-Feb-2015/ 0 subjects	Assessment of ALK rearrangement determined with a validated test. The inclusion and exclusion criterion was amended accordingly.	To comply with FDA request
Amendment 2/ 11-Sep-2015/ 10 subjects	A new cohort (Cohort 4) was implemented to enroll subjects with MET mutations, irrespective of MET amplification status.	To assess the activity of capmatinib in MET-mutated NSCLC in light of emerging data showing that NSCLC subjects harboring MET mutations can benefit from treatment with MET inhibitors.
	Photosensitization: precautionary measures against ultraviolet exposure were included.	Nonclinical data suggested photosensitization potential of capmatinib
	Dose modification guidelines for hepatotoxicity were modified. Specific work-up guidelines for potential drug-induced liver injury (DILI) cases were added to the protocol. The dose modification rules as well as the follow-up evaluations for hepatic toxicities were also updated accordingly.	In Study Study X2202, a female subject experienced a serious, unexpected, possibly related AE of abnormal liver function tests during treatment with a combination of capmatinib and gefitinib. The Investigator assessed the AE as suspected to be related to the combination of capmatinib and gefitinib. This AE met the criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination. This triggered the dose modification guidelines for hepatotoxicity.
Amendment 3/ 28-Jul-2016/ 148 subjects	To further investigate and better characterize the optimal GCN as predictor of response to capmatinib. The following 2 subcohorts were implemented within Cohort 1 (Cohort 1: Subjects with a MET GCN of ≥ 6): • Subcohort 1a (referred to as Cohort 1a in the CSR): Subjects with a MET GCN of ≥ 10, or • Subcohort 1b (referred to as Cohort 1b in the CSR): Subjects with a MET GCN of ≥ 6 and < 10	To ensure an adequate representation of NSCLC subjects with very high amplified disease avoiding the uneven enrichment in the lower GCN range of this cohort, as the prevalence of MET amplification in NSCLC is known to diminish with the increase in GCN.

Amendment number/Date/ No of subjects enrolled at the time of amendment	Key protocol changes	Main rationale for amendment
	Restrictions on the use of PPIs as concomitant medications were removed.	The impact on the 12-hour post-dose concentration of capmatinib was minimal with only a ~7% reduction after rabeprazole treatment (Study A2101) and therefore, the concomitant use of PPIs is unlikely to impact the efficacy of capmatinib.
Amendment 4/ 17-Nov-2016/ 157 subjects	A new cohort (Cohort 5) was added to enroll treatment-naïve subjects with MET dysregulation: Cohort 5: Treatment-naïve subjects with MET dysregulation: •Subcohort 5a (referred to as Cohort 5a in the CSR): Subjects with a MET GCN ≥ 10 (without MET mutations) •Subcohort 5b (referred to as Cohort 5b in the CSR): Subjects with MET mutations regardless of MET GCN	To investigate the safety and antitumor activity of capmatinib in treatment-naïve NSCLC subjects harboring MET exon 14 skipping mutations or very high MET gene amplification (GCN ≥ 10 without MET mutations)
Amendment 5/ 13-Feb-2018/ 270 subjects	A new expansion Cohort 6 was added for enrollment of additional 30 subjects approximately with advanced NSCLC pretreated with one prior line of systemic therapy harboring either MET amplification (GCN ≥ 10) or MET mutations (irrespective of MET GCN).	To generate supportive safety and efficacy data in this second-line subject population, which accounted for the majority of subjects enrolled in the respective Cohort 1a and Cohort 4 and therefore Cohort 6 is considered representative of the overall eligible subject population of pretreated MET high amplified and mutated NSCLC.
	Exclusion criteria, the list of prohibited medications, the list of medications to be used with caution and the criteria for dose modifications were updated	Updated with main focus on pneumonitis/ILD events that were reported with capmatinib monotherapy and with results from the DDI studies Study A2102, Study A2103, and Study A2105.
Amendment 6/ 28-Feb-2019/ 330 subjects	A new expansion Cohort 7 was added for the enrollment of approximately 27 treatment-naïve subjects with advanced NSCLC harboring MET exon 14 skipping mutations (regardless of MET GCN).	The new Cohort 7 would allow the generation of additional supportive safety and efficacy data in this first line patient population, which currently accounts for the subjects enrolled in Cohort 5b of this study.
	Close the recruitment of NSCLC subjects with GCN ≥ 10 in Cohort 5a and Cohort 6	Due to enrollment hurdles and to very low prevalence of subjects with GCN≥ 10.

The FDA's Assessment:

FDA agrees with the summary of changes in the amendments listed above.

8.1.2. Study Results

The primary evidence of efficacy for capmatinib in MET mutated NSCLC as presented in this NDA submission is based on the Cohorts 4 (2nd/3rd line pretreated) and 5b (first line/treatment naive) from Study A2201.

Compliance with Good Clinical Practices

Data and The Applicant's Position:

The study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) to good clinical practice (GCP).

The FDA's Assessment:
FDA agrees with the applicant position.

Financial Disclosure

Data and The Applicant's Position:

Novartis has adequately disclosed any financial interests/arrangements with clinical investigators in accordance with the guidance for industry. Details of financial disclosure are presented in Section 19.2.

The FDA's Assessment:
FDA agrees with the applicant position. Please refer to section 19.2 for additional details.

Subject Disposition

Data:

Disposition of subjects in Cohort 4 and Cohort 5b, along with subjects in all the cohorts are presented in Table 25.

Table 25 : Subject Disposition (FAS) - Study CINC280A2201

	Cohort 4 (2nd/3rd line, MET mutated)	Cohort 5b (treatment-naïve, MET mutated)	All subjects[1]
	N=69	N=28	N=334
	n (%)	n (%)	n (%)
Treatment phase			
Ongoing[2]	8 (11.6)	9 (32.1)	48 (14.4)
Discontinued from treatment phase	61 (88.4)	19 (67.9)	286 (85.6)
Entered post-treatment follow-up	22 (31.9)	6 (21.4)	84 (25.1)
Entered survival follow-up	30 (43.5)	10 (35.7)	167 (50.0)
Discontinued from study	9 (13.0)	3 (10.7)	35 (10.5)
Primary reason for discontinuation from treatment phase			
Progressive disease	38 (55.1)	11 (39.3)	196 (58.7)
Adverse event	14 (20.3)	6 (21.4)	52 (15.6)
Physician decision	5 (7.2)	2 (7.1)	22 (6.6)
Subject/guardian decision	4 (5.8)	0	13 (3.9)
Death	0	0	2 (0.6)
Protocol deviation	0	0	1 (0.3)
Post-treatment follow-up			
Ongoing[2]	3 (4.3)	2 (7.1)	8 (2.4)
Discontinued from post-treatment follow-up	19 (27.5)	4 (14.3)	76 (22.8)
Entered survival follow-up after discontinuation from post-treatment follow-up	12 (17.4)	2 (7.1)	49 (14.7)
Discontinued from study	7 (10.1)	2 (7.1)	27 (8.1)
Primary reason for discontinuation from post-treatment follow-up			
Progressive disease	13 (18.8)	3 (10.7)	43 (12.9)
Physician decision	4 (5.8)	1 (3.6)	17 (5.1)
Subject/guardian decision	0	0	11 (3.3)
Adverse event	2 (2.9)	0	3 (0.9)
Death	0	0	1 (0.3)
Lost to follow-up	0	0	1 (0.3)

[1] All subjects include subjects from Cohorts 1-6
[2] Subjects ongoing at the time of the data cut-off of 15-Apr-2019

The Applicant's Position:

A total of 334 subjects were enrolled in the study at the time of the data cut-off, of whom 69 subjects were in Cohort 4 and 28 Subjects in Cohort 5b. Disease progression was the primary reason for the end of treatment in both the cohorts (Table 25).

The FDA's Assessment:
FDA agrees with Novartis' analysis of patient disposition in study A2201.

Protocol Violations/Deviations

Data:

Protocol deviations that led to the exclusion of subjects from Per Protocol Set is provided in Table 26.

Table 26: Protocol deviations leading to the exclusion from per protocol set (FAS) - Study CINC280A2201

	Cohort 4 (2nd/3rd line, MET mutated)	Cohort 5b (treatment-naïve, MET mutated)	All subjects[1]
	N=69	N=28	N=334
	n (%)	n (%)	n (%)
Patients with at least one protocol deviation	6 (8.7)	0	11 (3.3)
Selection criteria not met			
Patient has presence or history of a malignant disease other than NSCLC at study entry	1 (1.4)	0	4 (1.2)
Prior treatments criteria not met	2 (2.9)	0	3 (0.9)
RECIST criteria not met at baseline	2 (2.9)	0	3 (0.9)
Baseline ECOG performance status criteria not done or not met	1 (1.4)	0	1 (0.3)

[1] All subjects include subjects from Cohorts 1-6
A patient with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category

The Applicant's Position:

Protocol deviations were infrequent; 8.7% subjects in Cohort 4 and none in Cohort 5b were excluded from PPS (Table 26).

The FDA's Assessment:
Although it is challenging to ascertain the impact of protocol violations in single arm trials with small sample sizes, this clinical reviewer agrees with Novartis' conclusion that the protocol

deviations described above did not materially alter the assessment of safety or effects on objective response rate and duration of response for capmatinib in patients with MET exon-14 skipping NSCLC.

Demographic Characteristics
Data:

Demographic characteristics of Cohorts 4 and 5b, along with subjects in all the cohorts are presented in Table 27.

Table 27: Demographic and baseline characteristics (FAS) - Study CINC280A2201

Demographic variable	Cohort 4 (2nd/3rd line, MET mutated) N=69	Cohort 5b (treatment-naïve, MET mutated) N=28	All subjects[1] N=334
Age (years)			
n	69	28	334
Mean (SD)	71.0 (8.32)	72.4 (7.02)	64.9 (10.12)
Median	71.0	71.0	66.0
Minimum, Maximum	49.0, 90.0	57.0, 86.0	33.0, 90.0
Age category (years)-n (%)			
<65	14 (20.3)	3 (10.7)	143 (42.8)
≥ 65 to <75	31 (44.9)	14 (50.0)	137 (41.0)
≥ 75 to <85	20 (29.0)	10 (35.7)	47 (14.1)
≥ 85	4 (5.8)	1 (3.6)	7 (2.1)
Sex-n (%)			
Male	29 (42.0)	10 (35.7)	197 (59.0)
Female	40 (58.0)	18 (64.3)	137 (41.0)
Race-n (%)			
Caucasian	49 (71.0)	24 (85.7)	248 (74.3)
Asian	19 (27.5)	4 (14.3)	81 (24.3)
Native American	1 (1.4)	0	2 (0.6)
Black	0	0	2 (0.6)
Unknown	0	0	1 (0.3)
Ethnicity-n (%)			
Japanese	11 (15.9)	2 (7.1)	45 (13.5)
Hispanic or Latino	2 (2.9)	1 (3.6)	23 (6.9)
East Asian	4 (5.8)	1 (3.6)	20 (6.0)
Russian	1 (1.4)	4 (14.3)	10 (3.0)

Demographic variable	Cohort 4 (2nd/3rd line, MET mutated) N=69	Cohort 5b (treatment-naïve, MET mutated) N=28	All subjects[1] N=334
Chinese	2 (2.9)	0	9 (2.7)
West Asian	0	0	5 (1.5)
Mixed Ethnicity	2 (2.9)	0	4 (1.2)
South Asian	1 (1.4)	0	2 (0.6)
Southeast Asian	0	0	1 (0.3)
Other	35 (50.7)	18 (64.3)	178 (53.3)
Unknown	11 (15.9)	2 (7.1)	37 (11.1)
ECOG performance status-n (%)			
0	16 (23.2)	7 (25.0)	98 (29.3)
1	52 (75.4)	21 (75.0)	235 (70.4)
≥ 2	1 (1.4)	0	1 (0.3)
Smoking history-n (%)			
Never smoked	40 (58.0)	18 (64.3)	104 (31.1)
Ex-smoker	27 (39.1)	9 (32.1)	193 (57.8)
Current smoker	2 (2.9)	1 (3.6)	37 (11.1)

[1]All subjects include subjects from Cohorts 1-6.

The Applicant's Position:

Overall, subjects enrolled across all cohorts into this study had baseline characteristics indicative of subjects with advanced NSCLC; there was a higher prevalence of men (59.0%) and the majority were ex- smokers (57.8%), and with good ECOG status (99.7% had ECOG PS 0 or 1). The median age of subjects was 66 years (range: 33-90). Subjects with MET-mutated NSCLC (Cohorts 4 and 5b) were older (median age: 71 years) than the non-MET mutated subjects, with a predominance of females and never-smokers in this group (Table 27).

The FDA's Assessment:

FDA agrees with Novartis' analysis and assessment of the demographic characteristics in study A2201.

Other Baseline Characteristics

Data:

Disease history of subjects in Cohort 4, Cohort 5b, along with subjects in all the cohorts are presented in Table 28.

Table 28 Disease characteristics (FAS) - Study INC280A2201

	Cohort 4 (2nd/3rd line, MET mutated)	Cohort 5b (treatment-naïve, MET mutated)	All subjects[1]
	N=69	N=28	N=334
Histology/cytology-n (%)			
Adenocarcinoma	53 (76.8)	25 (89.3)	274 (82.0)
Squamous cell carcinoma	6 (8.7)	2 (7.1)	31 (9.3)
Undifferentiated carcinoma	1 (1.4)	0	7 (2.1)
Large cell carcinoma	1 (1.4)	0	6 (1.8)
Adenosquamous cell carcinoma	2 (2.9)	0	5 (1.5)
Carcinosarcoma	1 (1.4)	0	3 (0.9)
Other	5 (7.2)	1 (3.6)	8 (2.4)
Metastatic site of cancer[2]-n (%)			
Lymph node	46 (66.7)	16 (57.1)	240 (71.9)
Bone	41 (59.4)	16 (57.1)	151 (45.2)
Brain	9 (13.0)	3 (10.7)	89 (26.6)
Adrenal	11 (15.9)	6 (21.4)	71 (21.3)
Liver	16 (23.2)	4 (14.3)	65 (19.5)
Lung	0	1 (3.6)	1 (0.3)
Other[3]	54 (78.3)	20 (71.4)	246 (73.7)
None	1 (1.4)	0	1 (0.3)
Number of metastatic sites[2]-n (%)			
0	1 (1.4)	0	1 (0.3)
1	5 (7.2)	3 (10.7)	31 (9.3)
2	10 (14.5)	11 (39.3)	69 (20.7)
3	14 (20.3)	3 (10.7)	66 (19.8)
>3	39 (56.5)	11 (39.3)	167 (50.0)
Stage at initial diagnosis-n (%)			
IA	2 (2.9)	0	11 (3.3)
IB	4 (5.8)	2 (7.1)	14 (4.2)
IIA	3 (4.3)	0	11 (3.3)
IIB	7 (10.1)	2 (7.1)	16 (4.8)
IIIA	2 (2.9)	2 (7.1)	37 (11.1)
IIIB	9 (13.0)	5 (17.9)	34 (10.2)

	Cohort 4 (2nd/3rd line, MET mutated)	Cohort 5b (treatment-naïve, MET mutated)	All subjects[1]
	N=69	N=28	N=334
IV	42 (60.9)	17 (60.7)	210 (62.9)
Missing	0	0	1 (0.3)
Time since initial diagnosis of primary site to the first study treatment (months)			
n	69	28	334
Mean (SD)	17.4 (24.65)	9.4 (16.56)	16.7 (19.25)
Median	11.1	2.2	11.3
Minimum, Maximum	1.6, 176.4	0.6, 80.8	0.6, 176.4
Stage at study entry-n (%)			
IIIB	2 (2.9)	0	6 (1.8)
IV	67 (97.1)	28 (100)	328 (98.2)
Number of target lesions at baseline based on BIRC assessment			
0	1 (1.4)	0	10 (3.0)
1	25 (36.2)	9 (32.1)	91 (27.2)
2	23 (33.3)	7 (25.0)	105 (31.4)
3	13 (18.8)	5 (17.9)	74 (22.2)
4	5 (7.2)	5 (17.9)	35 (10.5)
5	2 (2.9)	2 (7.1)	19 (5.7)

[1] All subjects include subjects from Cohorts 1-6.
[2] Using metastatic sites as collected in CRF page of diagnosis and extent of cancer.
[3] Other includes all sites other than bone, lymph node, liver, and brain.
Some metastatic sites are grouped together (Adrenal, bone, brain, Liver, Lung, Lymph nodes sites).

The Applicant's Position:

Tumor burden and profiles were considered, in general, to be representative of those typically seen in subjects with locally advanced or metastatic NSCLC. All subjects except one, had at least one metastatic site, and the majority of subjects had ≥ 3 metastatic sites, indicating the high disease burden in these patient populations (Table 28).

The FDA's Assessment:
FDA agrees with Novartis' analysis and assessment of the additional listed demographic characteristics in study A2201.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Data:

No formal summary statistics were measured for treatment compliance, although relative dose intensity (RDI) indicated that the majority of subjects received the study drug as planned. The median RDI was 96.4% (range: 13.0 to 100.6), and the majority of subjects (62.6%) had an RDI category from >90% to 110%.

The Applicant's Position:

Compliance was assessed by the Investigator/study personnel at each visit and the information was captured in the source document.

The FDA's Assessment:
FDA agrees with Novartis' statement.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Overall response rate by BIRC assessment
Table 29: Best overall response per BIRC assessment (FAS) - Study CINC280A2201

	Cohort 4 (2nd/3rd line, MET mutated)		Cohort 5b (treatment-naïve, MET mutated)	
	N=69		N=28	
	n (%)	95% CI[1]	n (%)	95% CI[1]
Best overall response				
Complete response (CR)	0 (0.0)		1 (3.6)	
Partial response (PR)	28 (40.6)		18 (64.3)	
Stable disease (SD)	25 (36.2)		8 (28.6)	
Non-CR/non-PD (NCRNPD)	1 (1.4)		0 (0.0)	
Progressive disease (PD)	6 (8.7)		1 (3.6)	
Not evaluable (NE)[2]	9 (13.0)		0 (0.0)	
Overall response rate (ORR: CR+PR)	28 (40.6)	(28.9, 53.1)	19 (67.9)	(47.6, 84.1)
Disease control rate (DCR: CR+PR+SD+NCRNPD)	54 (78.3)	(66.7, 87.3)	27 (96.4)	(81.7, 99.9)

[1] Exact binomial 95% confidence interval.
[2] 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 Applicant's Position:

The primary objective, ORR per BIRC, was met in subjects with MET-mutated NSCLC, irrespective of the line of treatment. In Cohort 4, the ORR was 40.6% (95% confidence interval (CI): 28.9, 53.1), with confirmed PR in 28 subjects (40.6%) and in Cohort 5b, the ORR was 67.9% (95% CI: 47.6, 84.1), with confirmed CR in 1 (3.6%) subject, PR in 18 subjects (64.3%) (Table 29)

The FDA's Assessment:

FDA agrees with Novartis' description of the study results. Note that FDA does not base efficacy conclusion on pre-specified thresholds for single arm studies. Instead, FDA's assessment is based on the observed magnitude and durability of the capmatinib treatment effect. Additionally, FDA does not consider disease control rate to be adequate endpoint for a marketing application review.

Supportive analysis- ORR per Investigator assessment

Data:

Table 30: Best overall response per Investigator assessment (FAS)- Study CINC280A2201

	Cohort 4 (2nd/3rd line, MET mutated) N=69		Cohort 5b (treatment-naïve, MET mutated) N=28	
	n (%)	**95% CI [1]**	**n (%)**	**95% CI [1]**
Best overall response				
Complete response (CR)	1 (1.4)		0 (0.0)	
Partial response (PR)	28 (40.6)		17 (60.7)	
Stable disease (SD)	22 (31.9)		10 (35.7)	
Non-CR/non-PD (NCRNPD)	2 (2.9)		0 (0.0)	
Progressive disease (PD)	7 (10.1)		1 (3.6)	
Not evaluable (NE) [2]	9 (13.0)		0	
Overall response rate (ORR: CR+PR)	29 (42.0)	(30.2, 54.5)	17 (60.7)	(40.6, 78.5)
Disease control rate (DCR: CR+PR+SD+NCRNPD)	53 (76.8)	(65.1, 86.1)	27 (96.4)	(81.7, 99.9)

[1] Exact binomial 95% confidence interval.

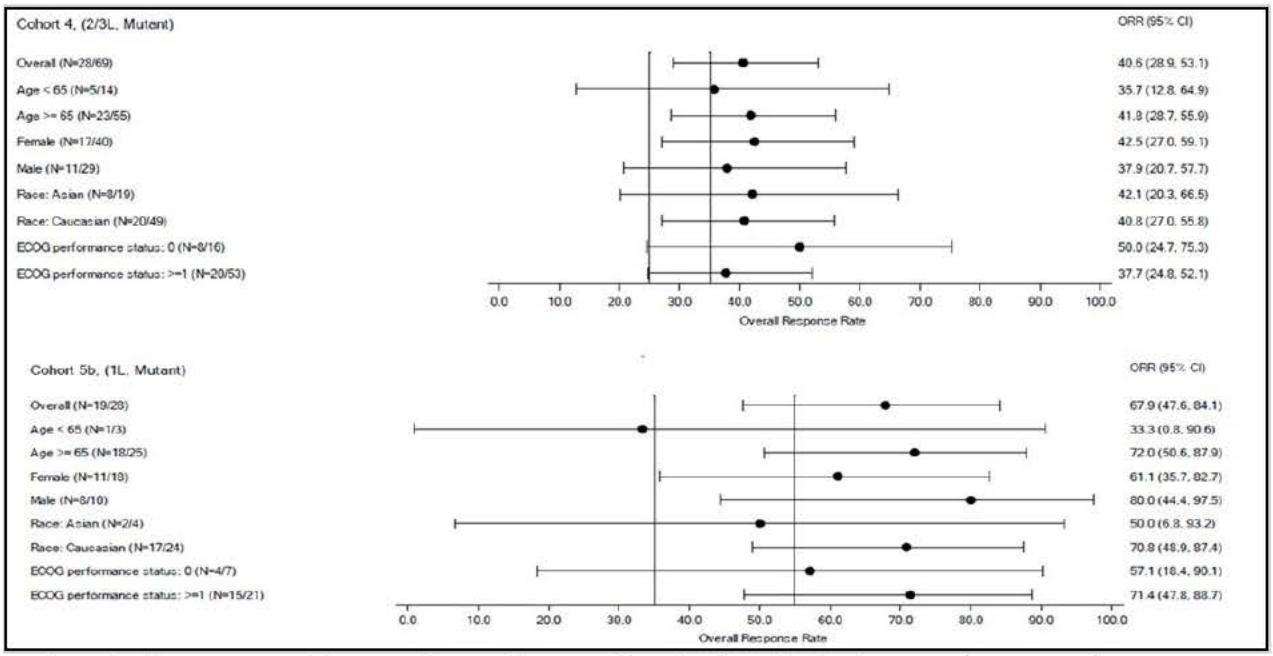
[2] Unknown (as per RECIST 1.1) i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks.

The results of ORR based on Investigator assessment supported the primary ORR analysis based on BIRC assessment (ORR per Investigator was 42.0% (95% CI: 30.2, 54.5) in Cohort 4, with

confirmed CR in one subject (1.4%) and confirmed PR in 28 subjects (40.6%) and 60.7% (95% CI: 40.6, 78.5) in Cohort 5b, with confirmed PR reported in 17 subjects (60.7%) (Table 30).

Subgroup analyses

Figure 8 : Forest plot of ORR by BIRC assessment by subgroup (FAS) - Study INC280A2201



Within the limitation of the small sample size of each identified subgroup (age, gender, race, ECOG PS), consistent treatment effects (measured as ORR by BIRC) were observed across subgroups evaluated in both Cohort 4 and Cohort 5b (Figure 8).

Data Quality and Integrity

No data integrity concerns were reported following completion of the site inspections. Investigator site audits were conducted in Japan (Site 1506), Spain (2205), Austria (3100), Republic of Korea (1601), and Germany (1306 and 1304).
The following Health authority GCP inspections were conducted:

- Center 1300, Prof. Jurgen Wolf, Koln, Germany was inspected by the Gesundheitsamt Dusseldorf from 08-Mar-2017 to 09-Mar-2017.
- Center 1315, Dr. Thomas Wehler, Homburg, Germany was inspected by the Ministerium für Soziales, Gesundheit, Frauen und Familie on 12-Oct-2017.
- Novartis Pharma GmbH, Germany was inspected by Regierung Von Oberfranken from 06-Nov-2017 to 09-Nov-2017.

Key secondary endpoint (duration of response per BIRC assessment) and other efficacy

secondary endpoints

Table 31: Summary of key and other secondary efficacy results (FAS) - Study CINC280A2201

	Cohort 4 (2nd/3rd line MET mutated)		Cohort 5b (treatment-naïve MET mutated)	
	N = 69	N = 69	N = 28	N = 28
	BIRC assessment	Investigator assessment	BIRC assessment	Investigator assessment
Key Secondary efficacy endpoint				
Median DOR[2], months (95% CI)	9.72 (5.55, 12.98)	8.31 (4.34, 12.06)	11.14 (5.55, NE)	13.96 (4.27, NE)
% responders with DOR ≥ 6 months	64.3	58.6	68.4	76.5
% responders with DOR ≥ 12 months	21.4	27.6	36.8	47.1
Other efficacy endpoints				
Median TTR (by descriptive statistics), months (range)	1.4 (1.2 to 3.8)	1.4 (1.2 to 3.3)	1.4 (1.3 to 6.9)	1.4 (1.2 to 4.0)
DCR, n (%) (95% CI[1])	54 (78.3) (66.7, 87.3)	53 (76.8) (65.1, 86.1)	27 (96.4) (81.7, 99.9)	27 (96.4) (81.7, 99.9)
Median PFS[2], months (95% CI)	5.42 (4.17; 6.97)	4.80 (4.11, 7.75)	9.69 (5.52, 13.86)	11.14 (5.52, 15.24)
Median OS[2], months (95% CI)	13.57 (8.61, 21.19)		15.24 (12.22, NE)	

[1] Clopper and Pearson exact binomial 95% confidence Interval

[2]Based on Kaplan-Meier estimate

BIRC = blinded independent review committee; CI = confidence interval; DCR = disease control rate; DOR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTR = time to response

The observed clinical benefit demonstrated as responses (CR or PR) was durable irrespective of the line of therapy (and was evident in both the pretreated and treatment-naïve settings). Tumor responses to capmatinib were rapid with a median TTR per BIRC of approximately 7 weeks, corresponding to the time of the first post-baseline tumor assessment, irrespective of the line of treatment. Time to response per Investigator assessment was consistent with that of the BIRC assessment (Table 30: Best overall response per Investigator assessment (FAS)- Study CINC280A2201).

Investigator-assessed PFS results were similar to the BIRC assessments (Table 31).

OS data are not yet mature. The median OS was 13.57 months (95% CI: 8.61, 21.19) in cohort 4 and 15.24 months (95% CI: 12.22, NE) in Cohort 5b (Table 31).

Dose/Dose Response

Data and the Applicant's Position:

No dose-response analysis was conducted for clinical efficacy endpoints as only 400 mg b.i.d. capmatinib tablets was tested in Study A2201.

The FDA's Assessment:

FDA agrees with Novartis' description of the results from supportive analyses. Results from these analyses showed consistent treatment effects (measured as ORR by BIRC) across subgroups. PFS and OS are difficult to not interpretable in a non-randomized open-label trial. The DOR results presented in this section are based on 15 April 2019 data cut-off date. Updated DOR results based on the 28 October 2019 data cut-off date are discussed in the next section.

FDA agrees that there were no major data integrity concerns in this application.

Durability of Response

Data: Duration of response data (DOR) is presented in Table 31 provided above and in Figures below.

Figure 9: Kaplan Meier plot of duration of response per BIRC assessment in Cohort 4 (FAS)- Study INC280A2201

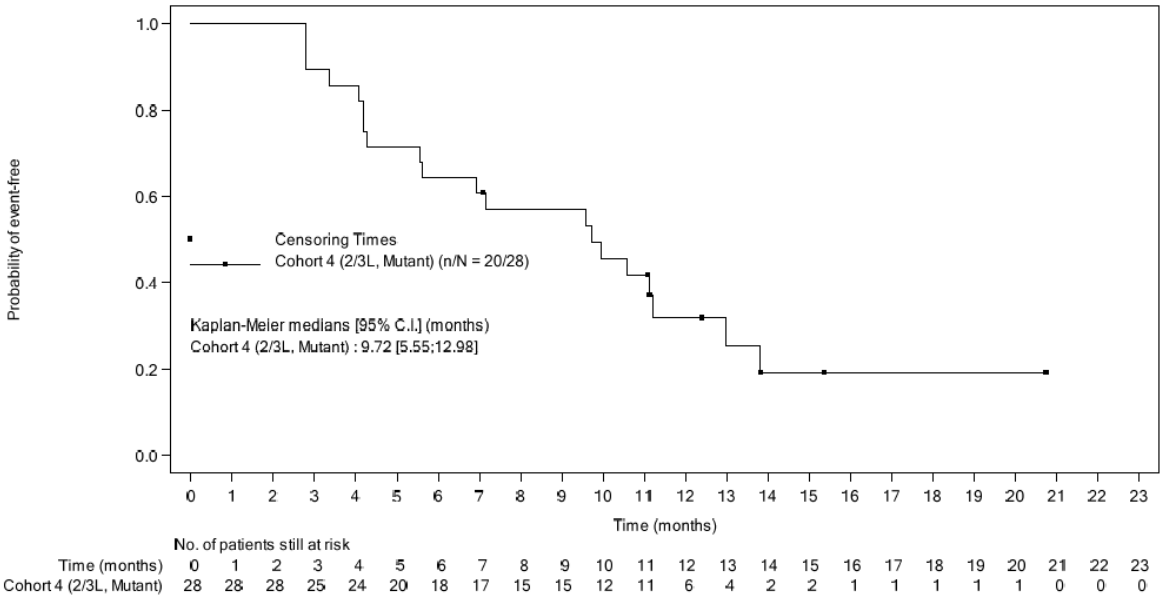
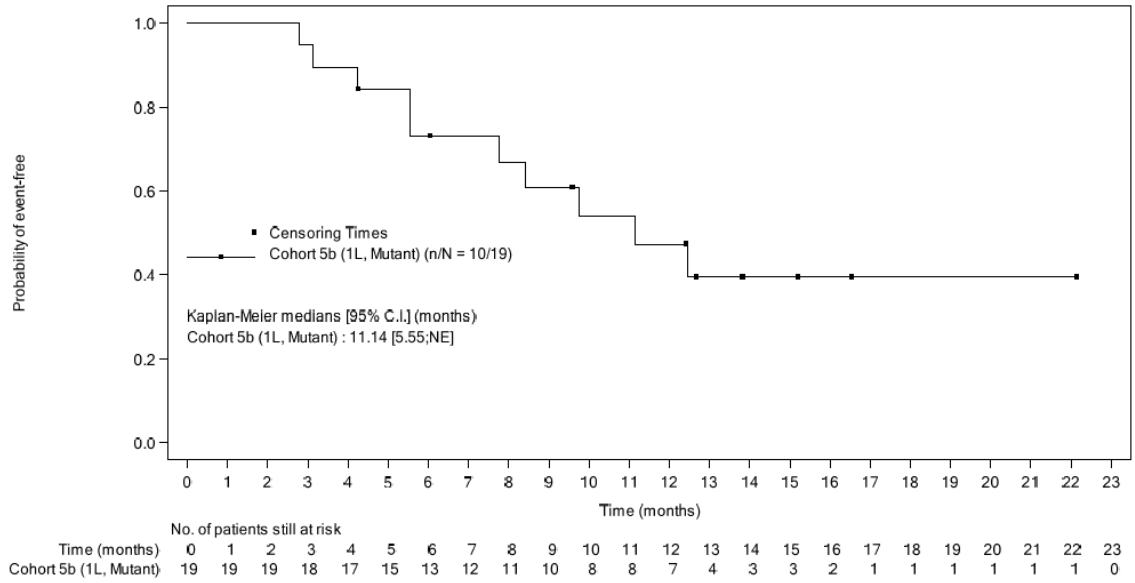


Figure 10: Kaplan Meier plot of duration of response per BIRC assessment in Cohort 5b (FAS)- Study INC280A2201



<u>The Applicant's Position:</u>

The durability of the responses seen with capmatinib irrespective of the line of therapy (in both the pretreated and treatment-naïve settings) further confirms that capmatinib is highly active against the molecular driver MET mutation, and corroborates the clinical relevance of an effective treatment option in this difficult-to-treat population of MET-mutated NSCLC and in the context of the limited viability of available therapies.

The FDA's Assessment:

The results presented in this section by Novartis were based the data with the cut-off date of 15 April 2019. FDA agrees with the results presented in this section. At the 15 April 2019 data cut-off date, the median DOR was 9.7 (5.5, 12.9) months and 11.1 (5.5, NE) months for the patients enrolled in Cohort 4 and Cohort 5B who achieved confirmed CR or PR.

At the 28 October 2019 data cut-off, there were 6 subjects (21.43% of 28 responders) with ongoing response in Cohort 4 (2L/3L) and 7 subjects (36.8% of 19 responders) with ongoing response in Cohort 5B (1L).

Persistence of Effect

Data and the Applicant's Position:

Treatment with capmatinib should continue for as long as clinical benefit is evident, or until unacceptable toxicity occurs. Following discontinuation of therapy, the natural course of the disease, i.e. progression, can be expected.

The FDA's Assessment:

FDA agrees with the Novartis' position.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient reported outcomes

Data:

The median time to definitive deterioration (by Kaplan-Meier methodology) for the global health status/QoL was 12.39 months (95% CI: 4.21, 20.21) in Cohort 4 and 12.4 months (95% CI: 6.93, NE) in Cohort 5b.

The Applicant's Position:

Patient-reported outcome endpoints suggested that treatment with capmatinib maintained quality of life as well as general health status when compared to baseline.

The FDA's Assessment:

FDA considers the analyses of patient-reported outcome (PRO) endpoints to be exploratory in this study. No claims can be made based on these analyses. PROs and time-to-event endpoints such as time to definitive deterioration are difficult to interpret in non-randomized open-label trials.

Additional Analyses Conducted on the Individual Trial

Text to be added should such analyses be requested.

The FDA's Assessment:
Not applicable

8.1.3. Supportive efficacy results

Supportive evidence of capmatinib efficacy in MET mutated NSCLC is provided from the studies X2102 and RWE X2401.

Data:

Study X2102

In addition to the efficacy data from Study A2201, supportive evidence of the efficacy of capmatinib in MET-mutated NSCLC was generated in Study X2102. Study design and endpoints of the studies are provided in Table 2.

Of the 55 subjects with NSCLC enrolled, 4 subjects were identified with MET mutations. All 4 of these subjects showed tumor reductions per BIRC including 1 confirmed complete response (CR), 2 confirmed partial responses (PR), and one stable disease (SD) per RECIST 1.1.
No pooling of efficacy data, nor direct comparisons between Studies A2201 and X2102 were performed due to key differences in the subject populations. The expansion part of Study X2102 enrolled subjects with different types of solid tumors, not only NSCLC, and most subjects were heavily pretreated with several lines of systemic therapy. Furthermore, study X2102 enrolled mainly subjects with MET-overexpressing/amplified NSCLC whereas MET mutation was assessed retrospectively only in subjects with available tumor samples. Additionally, the small number of subjects with MET-mutated NSCLC enrolled in Study X2102 (n=3) limited the value of a combined efficacy analysis between the two studies.

Study X2401

This application also includes data from real-world evidence (RWE) (Study CINC280X2401), global retrospective chart collection to describe the natural history of advanced MET-dysregulated NSCLC, including data from 157 patients with MET-mutated advanced NSCLC. The main findings in terms of demographics and disease characteristics in the MET mutated NSCLC subjects were as follows:

- Consistent with prior reports (Schrock et al 2016, Awad et al 2019), MET mutated advanced NSCLC is diagnosed in older subjects compared to unselected advanced NSCLC population (median age 73 years compared to ~60 years old in MET unselected advanced NSCLC).
- No substantial difference in gender distribution was observed (50.3% male vs 49.7% female).
- MET mutated NSCLC seems to occur irrespective of smoking history (56.1% ex/current smokers vs 40.8% never smokers) and tumor histology (adenocarcinoma 75.8%, squamous cell carcinoma 5.1%).
- At the time of their initial diagnosis, 32.4% of MET-mutated subjects presented with brain metastases and 59.3% had bone metastases.
- 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, 61.0%% of the subjects with MET-mutated NSCLC included in this RWE expressed high PD-L1 levels (>50%).

RWE findings is clinically significant and fills an unmet medical need in the context of the limited treatment options available for this difficult-to-treat population of elderly subjects with poor prognosis. Furthermore, the lack of efficacy of IO, as previously reported in other molecularly selected subsets of NSCLC, and the overall frailty of subjects with MET-mutated NSCLC which limit the feasibility and overall benefit of the currently available IO-based multi drug combinations, further strengthen the clinical relevance of the efficacy of capmatinib irrespective of the line of treatment.
The main findings describing the prognostic and predictive role of MET mutation is presented in Table 32.

Table 32: Summary of key efficacy results – Study CINC280X2401

	First-line		Second-/third-line	
	Platinum-based	IO	IO	Single-agent chemotherapy
	N = 86	N = 17	N = 24	N = 22
Overall response rate – n (%) (95% CI)	22 (25.6) (16.8, 31.6)	6 (35.3) (14.2, 61.7)	4 (16.7) (4.7, 37.4)	3 (13.6) (2.9, 34.9)
Best overall response – n (%)				
Complete response	1 (1.2)	1 (5.9)	0	0
Partial response	21(24.4)	5 (29.4)	4 (16.7)	3 (13.6)
Stable disease	20 (23.3)	3 (17.6)	5 (20.8)	4 (18.2)
Progressive disease	27 (31.4)	5 (29.4)	9 (37.5)	8 (36.4)
Other	5 (5.8)	1 (5.9)	3 (12.5)	3 (13.6)
Unknown	12 (12.8)	2 (11.8)	3 (12.5)	4 (18.2)
Progression free survival				
No. of events – n (%)	83 (96.5)	13 (76.5)	24 (100)	20 (90.9)
No. censored – n (%)	3 (3.5)	4 (23.5)	0	2 (9.1)
Median (months) (95% CI)	5.1 (3.3, 6.9)	2.6 (1.0, 6.9)	3.1 (1.9, 4.1)	2.8 (1.2, 5.0)
Overall survival				
No. of events – n (%)	43 (70.5)	5 (41.7)	4 (44.4)	7 (43.8)
No. censored – n (%)	18 (29.5)	7 58.3)	5 (55.6)	9 (56.3)
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)

8.1.4. Integrated Review of Effectiveness

The FDA's Assessment:

Refer to Section 8.1.5 regarding assessment of efficacy across trials. This application is primarily supported by results from Study A2201. As of 28 October 2019, data cut-off, median DOR was 9.7 months (5.5, 12.9) for the patients in Cohort 4 and 12.6 months (5.5, 25.3) for patients in Cohort 5B. The responses were durable with 64% (44%, 81%) of the previously treated and 68% (43%, 87%) of the treatment-naïve responders achieving six months or longer response. Duration of response was more than 12 months for 32% (16%, 52%) of previously treated and 47% (24%, 71%) of treatment-naïve patients who achieved complete or partial response. Response was ongoing for six previously treated and seven treatment-naïve responders.

Sensitivity analyses demonstrated the robustness of the primary endpoint results. Subgroup analyses demonstrated the consistency of the results across various prespecified subgroups. Response rates were noticeably higher for elderly patients and for those who never smoked.

8.1.5. Assessment of Efficacy Across Trials

Data and the applicant's position:

Details of the efficacy results of registration study, Study A2201 are provided in Section 8.1.2. Supportive efficacy data from Studies Study X2102 and Study X2401 are provided in Section 8.1.3

Additional Efficacy Considerations

The FDA's Assessment:

No additional efficacy data are considered other than the data described in section 8.1.2 and 8.1.3.

While FDA considers data from Study X2102 and Study X2401 to be supportive, Novartis did not submit this data, and thus FDA cannot independently verify these results. Study X2102 included only 4 patients with MET exon 14 skipping mutation NSCLC. Study X2401 provided estimate of MET dysregulated NSCLC natural history via a global retrospective chart collection.

8.1.6. Integrated Assessment of Effectiveness

The Applicant's Position:

The efficacy evaluation for this submission is mainly based on the primary analysis of the MET mutation cohorts (Cohorts 4 and 5b) from Study A2201.

The study met its primary objective ORR by BIRC per Response Evaluation Criteria In Solid Tumors (RECIST 1.1) with evidence of clinical benefit of capmatinib in both the pretreated setting (Cohort 4), with an ORR of 40.6% (95% CI: 28.9, 53.1), and the treatment-naive setting (Cohort 5b), with an ORR of 67.9% (95% CI: 47.6, 84.1).

The key secondary endpoint (DOR by BIRC), the other secondary efficacy endpoints (DCR, PFS, and OS), and subgroup analyses (ORR by race, age, gender, and ECOG status) corroborated the robustness and consistency of the results. Tumor response was durable with the Kaplan-Meier

median DOR per BIRC of 9.72 months (95% CI: 5.55, 12.98) in Cohort 4 and 11.14 months (95% CI: 5.55, NE) in Cohort 5b. The DCR by BIRC in Cohort 4 was 78.3% and in Cohort 5b was 96.4%. The onset of the observed responses was rapid, occurring by the first post-baseline scan in most cases.

Median PFS by BIRC was 5.42 months (95% CI: 4.17, 6.97) in Cohort 4 and 9.69 months (95% CI: 5.52, 13.86) in Cohort 5b. While still immature at the time of this analysis, the data on OS show that capmatinib provides a clinically significant benefit for this patient population who have a poor baseline prognosis (median OS since the start of capmatinib was 13.57 months (95% CI: 8.61, 21.19) in Cohort 4 and 15.24 months (95% CI: 12.22, NE) in Cohort 5b). All efficacy analyses per Investigator were consistent with the analyses per BIRC.

In conclusion, primary results from Study A2201 show substantial, durable, and rapid antitumor response of capmatinib in subjects with MET-mutated NSCLC, irrespective of the line of therapy. The robustness of these results are supported by the secondary efficacy endpoints and subgroup analyses from Study A2201, along with the descriptive data from Studies X2102 and X2401. Capmatinib is clinically efficacious in treating patients who present with the challenging diagnosis of MET-mutated advanced/metastatic NSCLC.

The FDA's Assessment:

FDA agrees with Novartis' conclusion that primary results from Study A2201 show preliminary evidence of clinically meaningful and durable antitumor response of capmatinib in subjects with MET-mutated NSCLC, irrespective of the line of therapy. Progression-free survival and overall survival results are not interpretable in a single-arm study.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant's Position:

The data presented here is a comprehensive analysis of safety data from Study A2201 along with supportive safety data were generated from the pooled datasets of 6 single agent studies (Studies: A2201, X1101, X2102, A2108, A2103 (post drug-drug interaction (DDI) phase only) and A2105 (post-DDI phase only)). (Details of all the studies are provided in Table 23 of Section 7.1). These studies have been pooled based on the following criteria:
Treatment at the recommended dose (RD): Pooled studies included subjects treated with capmatinib monotherapy at the RD (400 mg tablet b.i.d. or 600 mg capsule b.i.d.); these two doses have been shown to be equivalent. The 400 mg b.i.d. dose (tablet formulation) is the targeted dosage for which approval is currently being sought.

Underlying disease: While the primary focus of this summary of clinical safety (SCS) is Study A2201 (which exclusively enrolled subjects with NSCLC, including MET exon 14 skipping NSCLC which is the indication sought for capmatinib), the remaining pooled studies included additional subjects with NSCLC together with subjects with other solid tumors thus allowing for larger datasets.
Study completion status: Studies that had achieved last-patient last-visit (LPLV) and were completed by 15-Apr-2019 (data cut-off date for the primary analysis of this submission) were included in these pooled analyses, with the exception of Study A2201 which remained ongoing at the time of such analysis.
Based on the aforementioned pooling criteria of subjects treated at the RD of either 400 mg tablet b.i.d. or 600 mg capsule b.i.d. and with the underlying disease condition, the supportive pooled safety data were grouped into: 1) All NSCLC subjects (N=419; of which 334 subjects were from Study A2201), 2) All solid tumor subjects (N=541).
To summarize, the safety of capmatinib in this report is primarily based on the safety data from Study A2201 (N=334 only NSCLC subjects, including MET mutated NSCLC), as the safety findings from this overall population are representative of the safety of the MET mutated cohorts.

The FDA's Assessment:
The clinical safety assessment of capmatinib is based primarily on data from study CINC280A2201 (A2201). The safety review of Study A2201 included review and analysis of the clinical study report (CSR), Novartis risk:benefit assessment, case report forms, selected narratives, the integrated summary of safety (ISS), and the primary datasets submitted by Novartis. The reviewers analyzed key safety datasets using several safety analysis queries and MedDRA based Adverse Events Diagnostics tool.

Subgroup analyses were performed as necessary to further characterize the safety profile of capmatinib including the adverse events of special interest (AESI). Adverse events occurring in patient treated with capmatinib from study A2201 were compared against pooled population treated at the recommended dose (400mg twice daily tablet or 600mg twice daily capsules) in all NSCLC (n=419, of which 334 patients were from study A2201) and in all solid tumor patients (n = 541).

The total population in study A2201 comprised 334 patients diagnosed with MET exon 14 skipping mutation NSCLC who received treatment with single agent capmatinib 400mg twice daily (tablet formation).

The supportive safety data in all NSCLC population were from pooled datasets of 6 single agent studies (Studies: A2201 (n=334), X1101 (n=5), X2102 (n=55), A2108 (n=11), [A2103 (n=7) (post drug-drug interaction (DDI) phase only)] and [A2105 (n=7) (post-DDI phase only)]. The additional supportive safety data in all solid tumor population were also pooled from the same datasets of 6 single agent studies (Studies: A2201 (n=334), X1101 (n=15), X2102 (n=105), A2108

(n=27), [A2103 (n=33) (post drug-drug interaction (DDI) phase only)] and [A2105 (n=26) (post-DDI phase only)].

The data cut-off dates were April 15, 2019 for the initial SCS and September 18, 2019 for the 120-day safety update. The results presented in this review are based on the initial safety data unless otherwise noted.

8.2.2. Review of the Safety Database

The safety data and analyses in the below sections include pooled safety data from "All solid tumor subjects" and from "All NSCLC subjects", the majority of which are from Study A2201.

Data:

Overall Exposure

Table 33: Duration of exposure to study treatment (Safety set)

	Study A2201	All NSCLC subjects	All solid tumor subjects
	N=334	N=419	N=541
Duration of exposure (weeks)			
Mean (SD)	25.8 (29.35)	24.5 (29.29)	21.2 (26.84)
Median (Min-Max)	14.9 (0.4-177.0)	13.1 (0.1-187.0)	10.4 (0.1-187.0)
Q1-Q3	6.3-34.4	6.1-32.1	6.0-25.4
Exposure categories - n (%)			
< 6 weeks	64 (19.2)	91 (21.7)	129 (23.8)
≥ 6 weeks	270 (80.8)	328 (78.3)	412 (76.2)
≥ 12 weeks	196 (58.7)	230 (54.9)	262 (48.4)
≥ 18 weeks	147 (44.0)	171 (40.8)	188 (34.8)
≥ 24 weeks	114 (34.1)	134 (32.0)	145 (26.8)
≥ 48 weeks	62 (18.6)	70 (16.7)	70 (12.9)
≥ 72 weeks	22 (6.6)	26 (6.2)	26 (4.8)
Subject-months	**1984.5**	**2357.8**	**2643.2**

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.

The Applicant's Position:

The overall exposure duration was sufficient to assess the safety of capmatinib monotherapy. In Study A2201 (as of the data cut-off date: 15-Apr-2019), the median exposure was 14.9 weeks (range: 0.4 to 177.0) (Table 33).

The FDA's Assessment:

FDA agrees with Novartis exposure analysis for patients enrolled in Study A2201. In study A2201, 334 patients received at least one dose of capmatinib. As shown in the table below, the median duration of treatment for patients in study A2201 is 14.9 weeks (range 0.4–177). Among patients who received capmatinib, 31% were exposed for at least 6 months and 16% were exposed for at least one year as shown in the table below.

Table 34: Summary of exposure, safety population in study A2201

Exposure	Trial Arm		
	Study A2201 N = 334 n (%)	**All NSCLC N = 419 n (%)**	**All Solid Tumor N = 541 n (%)**
Exposure duration (weeks) (AVAL)			
Mean (SD)	25.8 (29.3)	24.5 (29.3)	21.2 (26.8)
Median (Range)	14.9 (0.4–177)	13.1 (0.1–187)	10.4 (0.1–187)

Exposure	Trial Arm		
	Study A2201 N = 334 n (%)	**All NSCLC N = 419 n (%)**	**All Solid Tumor N = 541 n (%)**
Cumulatitive exposure (months			
< 6	230 (69)	298 (71)	410 (76)
6 - <12	51 (15)	61 (15)	71 (13)
>= 24	9 (2.7)	11 (2.6)	11 (2)
Less than 6 months	230 (69)	298 (71)	410 (76)
At least 6 months	104 (31)	121 (29)	131 (24)
At least 12 months	53 (16)	60 (14)	60 (11)

Table 34: Summary of exposure, safety population in study A2201

Exposure	Trial Arm		
	Study A2201 N = 334 n (%)	All NSCLC N = 419 n (%)	All Solid Tumor N = 541 n (%)
At least 24 months	9 (2.7)	11 (2.6)	11 (2)

Source: adex.xpt

Relevant characteristics of the safety population:

Data and The Applicant's Position:

Safety for the targeted indication has been derived primarily from Study A2201 comprising 334 subjects with EGFR-wt, ALK-negative rearrangement, locally advanced or metastatic NSCLC harboring MET mutations.
Overall, subjects enrolled into this study had baseline characteristics representative of subjects with advanced NSCLC; there was a higher prevalence of men (59.0%) than women (41.0%) and the majority were ex-smokers (57.8%), and with good ECOG status (99.7% had ECOG PS 0 or 1). The median age of subjects was 66 years (range: 33-90). Subjects with MET-mutated NSCLC (Cohorts 4 and 5b) were older (median age: 71 years) than the non-MET mutated subjects, with a predominance of females and never-smokers in this group (Table 27).

The FDA's Assessment:
FDA agrees with Novartis analysis of demographics of the safety population. The characteristics of the safety population of study A2201 are consistent with the epidemiology and natural history of patients with metastatic non-squamous NSCLC. There are no imbalances expected to influence assessments of safety. Patients with MET exon 14 skipping NSCLC (Cohorts 4 and 5b) were older (median age: 71 years) than the non-MET exon 14 skipping patients (median age: 65), with a predominance of females (60%) and never smokers (60%) in the MET exon 14 skipping NSCLC population.

Adequacy of the safety database:

Data and The Applicant's Position:

The proposed safety database is considered adequate for the detection and characterization of the overall safety of capmatinib monotherapy with more than 500 subjects with solid tumors

and to provide guidance regarding management of toxicities, and is also adequate for an assessment of the benefit-risk profile of capmatinib.

The FDA's Assessment:
FDA agrees that overall, the safety database of 334 capmatinib-treated patients with MET exon 14 skipping NSCLC, supportive safety data from 419 patients with metastatic NSCLC along with 541 patients in all solid tumor submitted by Novartis was adequate to evaluate safety given the established safety profile of capmatinib.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data and The Applicant's Position:

No meaningful safety concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow a thorough evaluation of safety. After completion of Investigator-site audits and Health Authority GCP inspections, no data integrity concerns were reported. Details of the inspections are provided in Section 8.1.2 under 'Data Quality and Integrity'.

The FDA's Assessment:
The data submitted was organized and adequate to perform a complete review of the safety of capmatinib. To assess the reliability and quality of the data, the clinical reviewer conducted random cross-validation of datasets with CRFs from study A2201; this assessment raised no concerns regarding data integrity. Overall, FDA agrees that there were no significant data quality or reporting issues identified during the review of this NDA. FDA did issue several information requests during the review cycle to obtain clarification and additional information regarding safety data included in the NDA.

Categorization of Adverse Events

The Applicant's Position:

AEs were coded using MedDRA version 22.0 and were graded using CTCAE version 4.03. If CTCAE grading did not exist for an AE, grades 1, 2, 3, or 4 corresponding to the intensity of mild, moderate, severe, and life-threatening, respectively, were used. Grade 5 (death) was not used in pooled studies, except Study A2108 (no grade 5 events were observed in study A2108); rather, information on any fatal outcome was collected from either one or more of the following eCRF pages: "Adverse event", "End of Treatment Phase completion", "End of post treatment phase Completion", or "Death".
The safety of capmatinib was evaluated on the basis of:

- Treatment emergent AEs, rate, type, and severity of AEs and causal relationship to treatment of AEs.
- Rate of deaths, SAEs, and AESIs.
- Treatment emergent AEs were AE collected from day of first dose of study drug to 30 days after last dose of study treatment
- Changes in laboratory parameters, with particular attention to grade 3 or 4 laboratory abnormalities (graded in accordance with the CTCAE version 4.03).
- Electrocardiogram (ECG) changes.

The FDA's Assessment:
FDA agrees with Novartis description of adverse events categorization. All AEs regardless of causality were collected up to 30 days after the last dose. Novartis' AEs were coded using MedDRA version 22.0 and were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0. For all TEAEs, the investigator provided his/her opinion regarding the relationship of the event to capmatinib. AEs were collected at every visit regardless of investigator-assessed relationship to study drug. All patients were followed until resolution or stabilization of any study-related AE. Safety assessments consisted of monitoring and recording of all AEs, including SAEs, urinalysis, vital signs, ECG, ECOG-PS, pregnancy test for females, and physical exams. Adverse events that started before the first dose but worsened during the treatment were considered to be on-treatment events.

Routine Clinical Tests

The Applicant's Position:

In Study A2201, safety assessments consisted of monitoring and recording all AEs, including all SAEs, the regular monitoring of hematology (at screening, day 1 and day 15 of Cycle 1, and day 1 of subsequent cycles), blood chemistry (at screening, day 1 and day 15 of Cycle 1, and day 1 of subsequent cycles), vital signs (at screening, day 1 and day 15 of Cycle 1, and day 1 of subsequent cycles), performance status (at screening, day 1 of Cycle 1, and day 1 of subsequent cycles), physical examinations, including pregnancy test (at screening, day 1 of Cycle 1, and day 1 of subsequent cycles, as applicable).

The FDA's Assessment:
FDA agrees that the schedule of assessments in A2201 was adequate to monitor and assess the safety of capmatinib in study A2201.

8.2.4. Safety Results

The FDA's Assessment:

Overall, the incidence of Grade 3 to 4 AEs, SAEs, AEs leading to withdrawal, and AEs leading to dose modifications/interruption was similar between the three-safety population. The incidence of deaths due to an AEs was highest in the all solid population (4.6%) and lowest in study A2201 arm (3.3%).

Table 35: Overview of Adverse Events

	Study A2201 N=334 (%)	All NSCLC N=419 (%)	All solid tumor N=541 (%)
No. of patients with one or more AEs	98	99	99
Grade 3 to 4	66	67	62
Serious AEs	51	50	48
Patients died due to AE	3.3	3.8	4.6
AE leading to Treatment Withdrawal	16	17	15
AE leading to dose modification/Interruption	59	59	56

Deaths

Data:

Table 36: Deaths (Safety set)

Preferred term	Study A2201	All NSCLC subjects	All solid tumor subjects
	N = 334	N = 419	N = 541
	n (%)	n (%)	n (%)
All deaths	215 (64.4)	236 (56.3)	261 (48.2)
Deaths within 30 days after the last dose [1]	53 (15.9)	65 (15.5)	82 (15.2)
Primary reason: Study indication	43 (12.9)	50 (11.9)	57 (10.5)
Primary reason: Other	10 (3.0)	15 (3.6)	25 (4.6)*
Cardiac arrest	2 (0.6)	2 (0.5)	2 (0.4)
Atrial fibrillation	1 (0.3)	1 (0.2)	1 (0.2)
Hepatitis	1 (0.3)	1 (0.2)	1 (0.2)
Pneumonia bacterial	1 (0.3)	1 (0.2)	1 (0.2)
Sepsis	1 (0.3)	1 (0.2)	1 (0.2)
Septic shock	1 (0.3)	1 (0.2)	1 (0.2)
Organising pneumonia	1 (0.3)	1 (0.2)	1 (0.2)

Preferred term	Study A2201	All NSCLC subjects	All solid tumor subjects
	N = 334	N = 419	N = 541
	n (%)	n (%)	n (%)
Pneumonitis	1 (0.3)	1 (0.2)	1 (0.2)
Respiratory distress	1 (0.3)	1 (0.2)	1 (0.2)
General physical health deterioration	0	1 (0.2)	4 (0.7)
Depressed level of consciousness	0	1 (0.2)	1 (0.2)
Non-small cell lung cancer	0	1 (0.2)	1 (0.2)
Adenocarcinoma	0	1 (0.2)	1 (0.2)
Cardio-respiratory arrest	0	1 (0.2)	1 (0.2)
Disease progression	0	0	2 (0.4)
Neurological decompensation	0	0	1 (0.2)
Penile cancer	0	0	1 (0.2)
Pleural effusion	0	0	1 (0.2)
Pneumonia	0	0	1 (0.2)
Respiratory tract infection	0	0	1 (0.2)

[1] from day of first dose of study drug to 30 days after last dose of study drug

*Although the total number of "Primary reason for deaths: others" in the above table and total number of "SAEs with fatal outcome" remains same (25 subjects), the subjects who are counted/included in these categories are different. The reason for this is explained below:
For two "on-treatment" deaths from Study A2103, the AE outcome was not collected as fatal and hence they were not counted under the category of "SAEs with fatal outcome. Two additional subjects were included: who had a fatal SAE but the death did not occur "on-treatment" and who had a fatal SAE, died "on-treatment"; but the death occurred after the cut-off 15-Apr-2019).

The Applicant's Position:

In Study A2201, of the 334 subjects, 215 subjects (64.4%) died, of which 53 were on-treatment deaths (15.9%) with 43 (12.9%) of these attributed to the underlying disease and 10 (3.0%) attributed to the following SAEs: cardiac arrest (2 subjects), and atrial fibrillation, hepatitis, pneumonia bacterial, pneumonitis, respiratory distress, organizing pneumonia, sepsis, and septic shock (1 subject each) (Table 36). Of these 10 deaths due to causes other than disease progression, 4 (cardiac arrest, hepatitis, organizing pneumonia, and pneumonitis) were suspected by the investigator to be related to the study drug (Table 36). Of these 4 deaths, only one was confirmed to be study-drug related by Novartis medical review. This subject had received thoracic radiotherapy, 37 days prior to study entry, and could be considered as a confounding factor.

The FDA's Assessment:

FDA reviewed all available death narratives of the patients in study A2201. Death due to AE was

reported for 16 patients (instead of 15 patients) in the all NSCLC safety population. Novartis reports that one death (patient A2201-(b) (6)) occurred 15 days after the data cut-off date in the original submission, however that death was captured under fatal SAEs at the time of the original submission. For the purposes of this review, FDA included the death of patient A2201-(b) (6) as part of the original submission. In general, fatal AEs were rare and in the pneumonitis case it was likely to be related to capmatinib. FDA agrees with the investigator assessment that cause of death could not be ascertained for the remaining of fatal deaths.

The fatal AEs were cardiac arrest (2), atrial fibrillation, hepatitis, pneumonia (3), pneumonitis, respiratory distress, sepsis, septic shock, adenocarcinoma, cardio-pulmonary arrest, depressed level of consciousness, general health deterioration, and NSCLC.

Table 37: Causes of Death in Safety Population in study A2201 and All NSCLC

	Study A2201 N=334	**All NSCLC N=419**
	Grade 5 N (%)	Grade 5 N (%)
On-treatment deaths	54 (16)	66 (16)
Underlying disease cause	43 (13)	50 (12)
All other reasons	11 (3.3)	16 (3.8)
Pneumonia	3 (0.9)	3 (0.7)
Cardiac arrest	2 (0.6)	2 (0.5)
Pneumonitis	1 (0.3)	1 (0.2)
Atrial fibrillation	1 (0.3)	1 (0.2)
Hepatitis	1 (0.3)	1 (0.2)
Respiratory distress	1 (0.3)	1 (0.2)
Sepsis	1 (0.3)	1 (0.2)
Septic shock	1 (0.3)	1 (0.2)
Adenocarcinoma	0	1 (0.2)
Cardio-pulmonary arrest	0	1 (0.2)
Depressed level of consciousness	0	1 (0.2)
General health deterioration	0	1 (0.2)
NSCLC	0	1 (0.2)

Serious Adverse Events

Data:

Table 38: Serious adverse events by preferred term (occurring in at least 1% in Study A2201/ All NSCLC subjects/All solid tumor subjects) (Safety set)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	**169 (50.6)**	**139 (41.6)**	**211 (50.4)**	**172 (41.1)**	**260 (48.1)**	**209 (38.6)**
Dyspnoea	23 (6.9)	17 (5.1)	28 (6.7)	21 (5.0)	28 (5.2)	21 (3.9)
Pneumonia	16 (4.8)	11 (3.3)	20 (4.8)	14 (3.3)	22 (4.1)	15 (2.8)
Pleural effusion	12 (3.6)	6 (1.8)	14 (3.3)	7 (1.7)	16 (3.0)	8 (1.5)
General physical health deterioration	10 (3.0)	9 (2.7)	13 (3.1)	12 (2.9)	21 (3.9)	20 (3.7)
Vomiting	8 (2.4)	5 (1.5)	11 (2.6)	6 (1.4)	16 (3.0)	10 (1.8)
Nausea	7 (2.1)	6 (1.8)	10 (2.4)	8 (1.9)	12 (2.2)	10 (1.8)
Abdominal pain	6 (1.8)	5 (1.5)	8 (1.9)	7 (1.7)	15 (2.8)	11 (2.0)
Pulmonary embolism	6 (1.8)	6 (1.8)	9 (2.1)	7 (1.7)	10 (1.8)	8 (1.5)
Cellulitis	5 (1.5)	3 (0.9)	6 (1.4)	3 (0.7)	7 (1.3)	4 (0.7)
Hyponatraemia	5 (1.5)	4 (1.2)	6 (1.4)	5 (1.2)	7 (1.3)	6 (1.1)
Pneumonitis	5 (1.5)	4 (1.2)	5 (1.2)	4 (1.0)	5 (0.9)	4 (0.7)
Respiratory failure	5 (1.5)	5 (1.5)	6 (1.4)	6 (1.4)	7 (1.3)	7 (1.3)
Respiratory tract infection	5 (1.5)	5 (1.5)	5 (1.2)	5 (1.2)	7 (1.3)	7 (1.3)
Cardiac failure	4 (1.2)	4 (1.2)	4 (1.0)	4 (1.0)	4 (0.7)	4 (0.7)
Lung infection	4 (1.2)	4 (1.2)	4 (1.0)	4 (1.0)	4 (0.7)	4 (0.7)
Non-cardiac chest pain	4 (1.2)	4 (1.2)	4 (1.0)	4 (1.0)	5 (0.9)	5 (0.9)
Oedema peripheral	4 (1.2)	3 (0.9)	4 (1.0)	3 (0.7)	4 (0.7)	3 (0.6)
Pyrexia	4 (1.2)	1 (0.3)	7 (1.7)	2 (0.5)	8 (1.5)	3 (0.6)
Asthenia	3 (0.9)	3 (0.9)	4 (1.0)	4 (1.0)	4 (0.7)	4 (0.7)
Diarrhoea	3 (0.9)	0	3 (0.7)	0	4 (0.7)	0
Dysphagia	3 (0.9)	2 (0.6)	3 (0.7)	2 (0.5)	3 (0.6)	2 (0.4)
Femur fracture	3 (0.9)	3 (0.9)	4 (1.0)	4 (1.0)	4 (0.7)	4 (0.7)
Pain in extremity	3 (0.9)	3 (0.9)	4 (1.0)	4 (1.0)	4 (0.7)	4 (0.7)
Pneumothorax	3 (0.9)	1 (0.3)	4 (1.0)	2 (0.5)	4 (0.7)	2 (0.4)

The Applicant's Position:

In Study A2201, SAEs were reported in 169 subjects (50.6%), including 139 subjects (41.6%) reporting SAEs of grade 3/4 severity. The most common SAEs (occurring in ≥ 2% of the subjects) were: dyspnea (23 subjects, 6.9%), pneumonia (16 subjects, 4.8%), pleural effusion (12 subjects, 3.6%), general physical health deterioration (10 subjects, 3.0%), vomiting (8 subjects, 2.4%), and nausea (7 subjects, 2.1%) (Table 38).

Treatment related SAEs

Data:

Table 39: Treatment related serious adverse events by preferred term (Safety set)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	**43 (12.9)**	**29 (8.7)**	**53 (12.6)**	**36 (8.6)**	**60 (11.1)**	**41 (7.6)**
Nausea	5 (1.5)	4 (1.2)	6 (1.4)	5 (1.2)	7 (1.3)	6 (1.1)
Vomiting	5 (1.5)	3 (0.9)	7 (1.7)	4 (1.0)	11 (2.0)	7 (1.3)
Diarrhoea	3 (0.9)	0	3 (0.7)	0	4 (0.7)	0
Oedema peripheral	3 (0.9)	2 (0.6)	3 (0.7)	2 (0.5)	3 (0.6)	2 (0.4)
Pneumonitis	3 (0.9)	3 (0.9)	3 (0.7)	3 (0.7)	3 (0.6)	3 (0.6)
Cellulitis	2 (0.6)	1 (0.3)	2 (0.5)	1 (0.2)	2 (0.4)	1 (0.2)
Decreased appetite	2 (0.6)	1 (0.3)	2 (0.5)	1 (0.2)	2 (0.4)	1 (0.2)
Hypoacusis	2 (0.6)	1 (0.3)	2 (0.5)	1 (0.2)	2 (0.4)	1 (0.2)
Interstitial lung disease	2 (0.6)	2 (0.6)	2 (0.5)	2 (0.5)	2 (0.4)	2 (0.4)
Peripheral swelling	2 (0.6)	0	2 (0.5)	0	2 (0.4)	0
Pleural effusion	2 (0.6)	0	2 (0.5)	0	2 (0.4)	0
Renal failure	2 (0.6)	0	2 (0.5)	0	2 (0.4)	0
Abdominal pain	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	3 (0.6)	2 (0.4)
Acute kidney injury	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Agitation	1 (0.3)	0	1 (0.2)	0	1 (0.2)	0
Amylase increased	1 (0.3)	1 (0.3)	2 (0.5)	2 (0.5)	2 (0.4)	2 (0.4)
Cardiac arrest	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Constipation	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Dehydration	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)
Dyspnoea	1 (0.3)	1 (0.3)	2 (0.5)	2 (0.5)	2 (0.4)	2 (0.4)
Febrile neutropenia	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
General physical condition abnormal	1 (0.3)	0	1 (0.2)	0	1 (0.2)	0
Generalised oedema	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Hepatic function abnormal	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Hepatitis	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Hepatotoxicity	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Hyponatraemia	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Infection	1 (0.3)	0	1 (0.2)	0	1 (0.2)	0
Liver function test abnormal	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Lung infection	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Malaise	1 (0.3)	1 (0.3)	2 (0.5)	1 (0.2)	3 (0.6)	2 (0.4)
Myocardial infarction	1 (0.3)	0	1 (0.2)	0	2 (0.4)	1 (0.2)
Organising pneumonia	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Pancreatitis acute	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Platelet count decreased	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Primary adrenal insufficiency	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Urticaria	1 (0.3)	0	1 (0.2)	0	1 (0.2)	0
Anaemia	0	0	0	0	1 (0.2)	1 (0.2)
Blood creatinine increased	0	0	1 (0.2)	0	2 (0.4)	1 (0.2)
Cerebral venous thrombosis	0	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Headache	0	0	1 (0.2)	0	1 (0.2)	0
Hypersensitivity	0	0	2 (0.5)	2 (0.5)	2 (0.4)	2 (0.4)
Lipase increased	0	0	0	0	1 (0.2)	1 (0.2)
Pericardial effusion	0	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)

The Applicant's Position:

With the exception of nausea and vomiting (5 subjects; 1.5% each), diarrhea, peripheral edema, and pneumonitis (3 subjects; 0.9% each), treatment-related SAEs were infrequently reported in either 1 or 2 subjects each (≤ 0.6%) (Table 39).

The FDA's Assessment:

Serious adverse reactions occurred in 51% of patients who received capmatinib. Serious adverse reactions in ≥ 2% of patients included dyspnea (7%), pneumonia (4.8%), pleural

effusion (3.6%), general physical health deterioration (3%), vomiting (2.4%), and nausea (2.1%). A fatal adverse reaction occurred in one patient (0.3%) due to pneumonitis as described previously. The table below summarizes the SAEs reported in ≥ 2% of patients in study A2201, all NSCLC, and all solid tumor populations.

Table 40: SAEs occurring in > 2 % of patients

	Study A2201 N=334 (%)	**All NSCLC N=419 (%)**	**All solid tumor N=541 (%)**
Total pts with at least one SAE	51	50	48
Dyspnea	7	7	5
Pneumonia	4.8	4.8	4.1
Pleural effusion	3.6	3.3	3
Physical health deterioration	3	3.1	3.9
Vomiting	2.4	2.6	3
Nausea	2.1	2.4	2.2

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 41: Adverse events leading to permanent discontinuation of study treatment by preferred term (occurring in at least 0.5% in Study A2201/ All NSCLC subjects/All solid tumor subjects) (Safety set)

	Study A2201		**All NSCLC subjects**		**All solid tumor subjects**	
	N=334		**N=419**		**N=541**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	**54 (16.2)**	**33 (9.9)**	**69 (16.5)**	**44 (10.5)**	**80 (14.8)**	**50 (9.2)**
Oedema peripheral	6 (1.8)	2 (0.6)	8 (1.9)	3 (0.7)	9 (1.7)	3 (0.6)
Pneumonitis	6 (1.8)	1 (0.3)	6 (1.4)	1 (0.2)	6 (1.1)	1 (0.2)
Fatigue	5 (1.5)	3 (0.9)	5 (1.2)	3 (0.7)	5 (0.9)	3 (0.6)
Alanine aminotransferase increased	3 (0.9)	2 (0.6)	4 (1.0)	2 (0.5)	4 (0.7)	2 (0.4)
Aspartate aminotransferase increased	3 (0.9)	2 (0.6)	3 (0.7)	2 (0.5)	3 (0.6)	2 (0.4)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Nausea	3 (0.9)	1 (0.3)	4 (1.0)	2 (0.5)	7 (1.3)	2 (0.4)
Vomiting	3 (0.9)	1 (0.3)	3 (0.7)	1 (0.2)	5 (0.9)	2 (0.4)
Blood bilirubin increased	2 (0.6)	0	2 (0.5)	0	2 (0.4)	0
Blood creatinine increased	2 (0.6)	0	3 (0.7)	0	3 (0.6)	0
General physical health deterioration	2 (0.6)	2 (0.6)	3 (0.7)	3 (0.7)	4 (0.7)	4 (0.7)
Interstitial lung disease	2 (0.6)	2 (0.6)	2 (0.5)	2 (0.5)	2 (0.4)	2 (0.4)
Organising pneumonia	2 (0.6)	1 (0.3)	2 (0.5)	1 (0.2)	2 (0.4)	1 (0.2)
Pneumonia	2 (0.6)	2 (0.6)	2 (0.5)	2 (0.5)	3 (0.6)	3 (0.6)
Hypersensitivity	0	0	2 (0.5)	2 (0.5)	2 (0.4)	2 (0.4)
Hypoalbuminaemia	0	0	2 (0.5)	1 (0.2)	2 (0.4)	1 (0.2)

The Applicant's Position:

In Study A2201, 54 subjects (16.2%) had AEs which led to permanent discontinuation of study treatment irrespective of study drug relation; with 9.9% (33 subjects) experiencing grade 3/4 AEs leading to permanent discontinuation of study treatment. The incidence of any specific AEs was < 2% and with the exception of peripheral edema and pneumonitis (1.8%; 6 subjects each), fatigue (1.5%; 5 subjects), and vomiting, ALT increased, AST increased, and nausea (0.9%; 3 subjects each); other AEs resulting in discontinuation of the study drug were reported in either 1 or 2 subjects.

The FDA's Assessment:

FDA agrees with Novartis' analysis of AEs that led to study drug discontinuation. The table below summarizes the adverse reactions leading to capmatinib interruption. Adverse reactions leading to interruption of capmatinib occurred in 16% of patients in study A2201; the most common (>1%) were peripheral edema (1.8%), pneumonitis (1.8%), and fatigue (1.5%).

Table 42: AEs leading to Treatment Withdrawal > 1%

	Study A2201 N=334 (%)	All NSCLC N=419 (%)	All solid tumor N=541 (%)
Total pts with at least one AE leading to treatment withdrawal	16	17	15
Peripheral edema	1.8	1.9	1.7
Pneumonitis	1.8	1.4	1.1
Fatigue	1.5	1.2	0.9

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 43: Adverse events requiring dose adjustment and/or interruption by preferred term (occurring in at least 1% in Study A2201/ All NSCLC subjects/All solid tumor subjects) (Safety set)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	**198 (59.3)**	**132 (39.5)**	**248 (59.2)**	**160 (38.2)**	**300 (55.5)**	**190 (35.1)**
Oedema peripheral	41 (12.3)	20 (6.0)	50 (11.9)	22 (5.3)	51 (9.4)	22 (4.1)
Blood creatinine increased	28 (8.4)	0	33 (7.9)	0	41 (7.6)	1 (0.2)
Nausea	23 (6.9)	4 (1.2)	32 (7.6)	5 (1.2)	41 (7.6)	7 (1.3)
Vomiting	22 (6.6)	3 (0.9)	32 (7.6)	4 (1.0)	37 (6.8)	6 (1.1)
Alanine aminotransferase increased	16 (4.8)	14 (4.2)	19 (4.5)	17 (4.1)	21 (3.9)	19 (3.5)
Lipase increased	15 (4.5)	15 (4.5)	17 (4.1)	17 (4.1)	19 (3.5)	19 (3.5)
Dyspnoea	13 (3.9)	4 (1.2)	17 (4.1)	7 (1.7)	17 (3.1)	7 (1.3)
Amylase increased	12 (3.6)	11 (3.3)	14 (3.3)	13 (3.1)	14 (2.6)	13 (2.4)
Aspartate aminotransferase increased	12 (3.6)	8 (2.4)	14 (3.3)	8 (1.9)	16 (3.0)	9 (1.7)
Fatigue	12 (3.6)	9 (2.7)	15 (3.6)	10 (2.4)	20 (3.7)	11 (2.0)
Decreased appetite	10 (3.0)	3 (0.9)	13 (3.1)	3 (0.7)	16 (3.0)	3 (0.6)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Blood bilirubin increased	7 (2.1)	0	7 (1.7)	0	11 (2.0)	2 (0.4)
Diarrhoea	7 (2.1)	1 (0.3)	10 (2.4)	1 (0.2)	11 (2.0)	1 (0.2)
Pneumonia	7 (2.1)	4 (1.2)	9 (2.1)	6 (1.4)	10 (1.8)	6 (1.1)
Asthenia	6 (1.8)	5 (1.5)	9 (2.1)	6 (1.4)	11 (2.0)	6 (1.1)
Cellulitis	5 (1.5)	2 (0.6)	5 (1.2)	2 (0.5)	5 (0.9)	2 (0.4)
Dysphagia	5 (1.5)	0	5 (1.2)	0	5 (0.9)	0
Lung infection	5 (1.5)	3 (0.9)	5 (1.2)	3 (0.7)	5 (0.9)	3 (0.6)
Pyrexia	5 (1.5)	0	6 (1.4)	0	8 (1.5)	1 (0.2)
Abdominal pain	4 (1.2)	2 (0.6)	5 (1.2)	3 (0.7)	11 (2.0)	5 (0.9)
Gamma-glutamyltransferase increased	4 (1.2)	2 (0.6)	4 (1.0)	2 (0.5)	4 (0.7)	2 (0.4)
General physical health deterioration	4 (1.2)	4 (1.2)	4 (1.0)	4 (1.0)	5 (0.9)	4 (0.7)
Platelet count decreased	4 (1.2)	3 (0.9)	4 (1.0)	3 (0.7)	4 (0.7)	3 (0.6)
Pneumonitis	4 (1.2)	0	4 (1.0)	0	4 (0.7)	0
Pleural effusion	3 (0.9)	0	4 (1.0)	1 (0.2)	5 (0.9)	1 (0.2)
Anaemia	3 (0.9)	3 (0.9)	4 (1.0)	4 (1.0)	4 (0.7)	4 (0.7)
Pulmonary embolism	3 (0.9)	2 (0.6)	4 (1.0)	2 (0.5)	5 (0.9)	3 (0.6)
Dyspepsia	2 (0.6)	0	5 (1.2)	0	5 (0.9)	0
Generalised oedema	2 (0.6)	2 (0.6)	4 (1.0)	3 (0.7)	4 (0.7)	3 (0.6)
Hypophosphataemia	2 (0.6)	2 (0.6)	4 (1.0)	4 (1.0)	5 (0.9)	5 (0.9)
Abdominal pain upper	1 (0.3)	0	4 (1.0)	0	7 (1.3)	0

The Applicant's Position:

In Study A2201, the majority of subjects (59.3%; 198 subjects) had ≥ 1 AE that required dose adjustment and/or interruption of the study treatment. The most common AEs leading to dose adjustment and/or interruption (occurring in ≥ 5% of subjects) were: peripheral edema (12.3%; 41 subjects), increased blood creatinine (8.4%; 28 subjects), nausea (6.9%; 23 subjects), and vomiting (6.6%; 22 subjects).

Grade 3/4 AEs requiring dose adjustment and/or interruption of study treatment were noted in 39.5% of subjects and the most common AEs (occurring in ≥ 3% of subjects) were: peripheral

edema (6.0%; 20 subjects), increased lipase (4.5%; 15 subjects), increased ALT (4.2%; 14 subjects), and increased amylase (3.3%; 11 subjects) (Table 43).

The FDA's Assessment:
Dose interruptions due to an adverse reaction occurred in 54% of patients who received capmatinib in study A2201, 55% in the all NSCLC population and 52% in the all solid tumor population. Adverse reactions requiring dosage interruption in > 2% of patients who received capmatinib included peripheral edema, increased blood creatinine, nausea, vomiting, increased lipase, increased ALT, dyspnea, increased amylase, increased AST, increased blood bilirubin, fatigue, and pneumonia.

Table 44: Adverse events requiring dose interruption by preferred term (> 2 %)

	Study A2201	
	N=334	
	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**
Number of subjects with at least one event	**181 (54)**	**120 (36)**
Peripheral edema	29 (9)	15 (4.5)
Blood creatinine increased	24 (7)	0 (0)
Nausea	18 (5)	4 (1.2)
Vomiting	18 (5)	3 (0.9)
Lipase increased	15 (4.5)	15 (4.5)
Increased ALT	13 (3.9)	11 (3.3)
Dyspnea	13 (3.9)	4 (1.2)
Amylase increased	11 (3.3)	10 (3)
Increased AST	10 (3)	7 (2.1)
Bilirubin increased	7 (2.1)	0 (0)
Fatigue	7 (2.1)	6 (1.8)
Pneumonia	7 (2.1)	4 (1.2)

Dose reductions due to an adverse reaction occurred in 23% of patients who received capmatinib. Adverse reactions requiring dosage reductions in > 2% of patients who received capmatinib included peripheral edema, increased ALT, increased blood creatinine, and nausea as demonstrated in the table below.

Table 45: Adverse events requiring dose reduction by preferred term (> 2 %)

	Study A2201	
	N=334	
	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**
Number of subjects with at least one event	**76 (23)**	**20 (6)**
Peripheral edema	24 (7)	8 (2.4)
ALT increased	10 (3)	3 (0.9)
Blood creatinine increased	7 (2)	0 (0)
Nausea	7 (2.1)	0 (0)

Significant Adverse Events

The Applicant's Position:

Significant AEs reported are described in other sections (deaths, SAEs, treatment related SAEs, AEs leading to permanent discontinuation, AEs requiring dose adjustment and/or interruption) of this document.

The FDA's Assessment:
FDA agrees that significant AEs are described in other sections.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 46: Adverse events irrespective of study drug relationship by preferred term (with an incidence greater than or equal to 5% in Study A2201/ All NSCLC subjects/All solid tumor subjects) (Safety set)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	**328 (98.2)**	**219 (65.6)**	**413 (98.6)**	**279 (66.6)**	**534 (98.7)**	**337 (62.3)**
Oedema peripheral	166 (49.7)	28 (8.4)	203 (48.4)	31 (7.4)	244 (45.1)	31 (5.7)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Nausea	147 (44.0)	9 (2.7)	190 (45.3)	12 (2.9)	245 (45.3)	15 (2.8)
Vomiting	94 (28.1)	8 (2.4)	124 (29.6)	11 (2.6)	164 (30.3)	15 (2.8)
Blood creatinine increased	85 (25.4)	0	102 (24.3)	0	120 (22.2)	1 (0.2)
Dyspnoea	81 (24.3)	23 (6.9)	106 (25.3)	28 (6.7)	120 (22.2)	29 (5.4)
Fatigue	72 (21.6)	16 (4.8)	95 (22.7)	18 (4.3)	127 (23.5)	23 (4.3)
Decreased appetite	69 (20.7)	3 (0.9)	91 (21.7)	5 (1.2)	122 (22.6)	6 (1.1)
Diarrhoea	61 (18.3)	1 (0.3)	80 (19.1)	3 (0.7)	107 (19.8)	4 (0.7)
Constipation	60 (18.0)	3 (0.9)	73 (17.4)	4 (1.0)	93 (17.2)	6 (1.1)
Cough	54 (16.2)	2 (0.6)	68 (16.2)	2 (0.5)	76 (14.0)	2 (0.4)
Back pain	47 (14.1)	3 (0.9)	60 (14.3)	4 (1.0)	71 (13.1)	7 (1.3)
Pyrexia	47 (14.1)	2 (0.6)	58 (13.8)	4 (1.0)	72 (13.3)	5 (0.9)
Alanine aminotransferase increased	42 (12.6)	19 (5.7)	52 (12.4)	24 (5.7)	65 (12.0)	27 (5.0)
Asthenia	41 (12.3)	12 (3.6)	58 (13.8)	16 (3.8)	75 (13.9)	17 (3.1)
Non-cardiac chest pain	34 (10.2)	4 (1.2)	41 (9.8)	5 (1.2)	46 (8.5)	7 (1.3)
Weight decreased	34 (10.2)	2 (0.6)	37 (8.8)	3 (0.7)	41 (7.6)	3 (0.6)
Anaemia	30 (9.0)	9 (2.7)	39 (9.3)	13 (3.1)	51 (9.4)	19 (3.5)
Pruritus	30 (9.0)	0	38 (9.1)	0	49 (9.1)	0
Amylase increased	29 (8.7)	12 (3.6)	39 (9.3)	18 (4.3)	39 (7.2)	18 (3.3)
Aspartate aminotransferase increased	29 (8.7)	10 (3.0)	36 (8.6)	13 (3.1)	51 (9.4)	15 (2.8)
Dizziness	29 (8.7)	1 (0.3)	37 (8.8)	1 (0.2)	45 (8.3)	1 (0.2)
Hypoalbuminaemia	29 (8.7)	2 (0.6)	42 (10.0)	6 (1.4)	52 (9.6)	6 (1.1)
Insomnia	27 (8.1)	0	32 (7.6)	0	41 (7.6)	0
Pneumonia	27 (8.1)	11 (3.3)	34 (8.1)	15 (3.6)	37 (6.8)	16 (3.0)
Headache	26 (7.8)	1 (0.3)	38 (9.1)	1 (0.2)	51 (9.4)	1 (0.2)
Lipase increased	26 (7.8)	18 (5.4)	33 (7.9)	21 (5.0)	37 (6.8)	23 (4.3)
Gamma-glutamyltransferase increased	24 (7.2)	9 (2.7)	26 (6.2)	10 (2.4)	32 (5.9)	13 (2.4)
Abdominal pain	23 (6.9)	6 (1.8)	30 (7.2)	8 (1.9)	46 (8.5)	12 (2.2)
Dyspepsia	23 (6.9)	0	31 (7.4)	0	49 (9.1)	0
Pain in extremity	23 (6.9)	3 (0.9)	28 (6.7)	4 (1.0)	32 (5.9)	4 (0.7)
Arthralgia	22 (6.6)	2 (0.6)	31 (7.4)	2 (0.5)	36 (6.7)	2 (0.4)
Pleural effusion	22 (6.6)	8 (2.4)	24 (5.7)	9 (2.1)	27 (5.0)	10 (1.8)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Abdominal pain upper	20 (6.0)	1 (0.3)	26 (6.2)	1 (0.2)	38 (7.0)	1 (0.2)
Muscle spasms	20 (6.0)	0	25 (6.0)	0	27 (5.0)	0
Nasopharyngitis	20 (6.0)	0	25 (6.0)	0	26 (4.8)	0
Blood alkaline phosphatase increased	19 (5.7)	0	21 (5.0)	1 (0.2)	25 (4.6)	3 (0.6)
Hypokalaemia	19 (5.7)	4 (1.2)	27 (6.4)	7 (1.7)	32 (5.9)	8 (1.5)
Musculoskeletal pain	19 (5.7)	2 (0.6)	28 (6.7)	2 (0.5)	28 (5.2)	2 (0.4)
Dysphagia	18 (5.4)	2 (0.6)	21 (5.0)	2 (0.5)	22 (4.1)	2 (0.4)
Hypophosphataemia	18 (5.4)	8 (2.4)	24 (5.7)	11 (2.6)	28 (5.2)	13 (2.4)
Musculoskeletal chest pain	18 (5.4)	3 (0.9)	19 (4.5)	3 (0.7)	20 (3.7)	3 (0.6)
Pulmonary embolism	18 (5.4)	11 (3.3)	22 (5.3)	13 (3.1)	24 (4.4)	14 (2.6)
Rash	18 (5.4)	1 (0.3)	24 (5.7)	1 (0.2)	32 (5.9)	1 (0.2)
Myalgia	17 (5.1)	1 (0.3)	18 (4.3)	1 (0.2)	23 (4.3)	1 (0.2)
General physical health deterioration	14 (4.2)	12 (3.6)	17 (4.1)	15 (3.6)	27 (5.0)	24 (4.4)

The Applicant's Position:

In Study A2201**,** the most frequently reported AEs by preferred terms, irrespective of study drug relationship (occurring in ≥ 20% of subjects) were: peripheral edema (49.7%; 166 subjects), nausea (44.0%; 147 subjects), vomiting (28.1%; 94 subjects), increased blood creatinine (25.4%; 85 subjects), dyspnea (24.3%; 81 subjects), fatigue (21.6%; 72 subjects), and decreased appetite (20.7%; 69 subjects) (Table 46).

Severity of AEs: Overall, 65.6% of subjects experienced grade 3/4 AEs in Study A2201 with 53.9% (180 subjects) having grade 3 AEs and 11.7% (39 subjects) having grade 4 AEs. The most frequently reported grade 3/4 AEs (in ≥ 5% of subjects) were: peripheral edema (8.4%; 28 subjects), dyspnea (6.9%; 23 subjects), increased ALT (5.7%; 19 subjects), and increased lipase (5.4%; 18 subjects).

Adverse drug reactions

Data:

Table 47: Adverse drug reactions - Study CINC280A2201 (Safety set)

System organ class ADR group	All grades	Frequency category All grades n(%)	Grade 3	Grade 4	Frequency category Grade 3/4	SAE	Leading to discontinuation
	n (%)		n (%)	n (%)		n (%)	n (%)
Infections and infestations							
Cellulitis	9 (2.7)	Common	3 (0.9)	0	Uncommon	5 (1.5)	
Metabolism and nutrition disorders							
Decreased appetite	69 (20.7)	Very common	3 (0.9)	0	Uncommon	2 (0.6)	1 (0.3)
Hyponatraemia	18 (5.4)	Common	10 (3.0)	1 (0.3)	Common	5 (1.5)	0
Hypophosphatemia	21 (6.3)	Common	6 (1.8)	2 (0.6)	Common	0	0
Respiratory, thoracic and mediastinal disorders							
Cough	54 (16.2)	Very common	2 (0.6)	0	Uncommon	2 (0.6)	0
Dyspnoea	81 (24.3)	Very common	21 (6.3)	2 (0.6)	Common	23 (6.9)	0
Interstitial lung disease and pneumonitis	15 (4.5)	Common	6 (1.8)	0	Common	7 (2.1)	8 (2.4)
Gastrointestinal disorders							
Acute pancreatitis	1 (0.3)	Uncommon	1 (0.3)	0	Uncommon	1 (0.3)	1 (0.3)
Amylase increased	29 (8.7)	Common	10 (3.0)	2 (0.6)	Common	1 (0.3)	1 (0.3)
Constipation	60 (18.0)	Very common	3 (0.9)	0	Uncommon	1 (0.3)	1 (0.3)
Diarrhoea	61 (18.3)	Very common	1 (0.3)	0	Uncommon	3 (0.9)	0
Lipase increased	26 (7.8)	Common	16 (4.8)	2 (0.6)	Common	0	
Nausea	147 (44.0)	Very common	9 (2.7)	0	Common	7 (2.1)	3 (0.9)
Vomiting	94 (28.1)	Very common	8 (2.4)	0	Common	8 (2.4)	3 (0.9)
Hepatobiliary disorders							
Alanine aminotransferase increased	42 (12.6)	Very common	17 (5.1)	2 (0.6)	Common	0	3 (0.9)

System organ class ADR group	All grades	Frequency category All grades n(%)	Grade 3	Grade 4	Frequency category Grade 3/4	SAE	Leading to discontinuation
Aspartate aminotransferase increased	29 (8.7)	Common	10 (3.0)	0	Common	0	3 (0.9)
Blood bilirubin increased	11 (3.3)	Common	2 (0.6)	0	Uncommon	0	2 (0.6)
Hypoalbuminemia	38 (11.4)	Very common	4 (1.2)	0	Common	0	0
Skin and subcutaneous tissue disorders							
Pruritus	33 (9.9)	Common	1 (0.3)	0	Uncommon	0	0
Urticaria	4 (1.2)	Common	2 (0.6)	0	Uncommon	1 (0.3)	1 (0.3)
Renal and urinary disorders							
Acute kidney injury	5 (1.5)	Common	1 (0.3)	0	Uncommon	3 (0.9)	
Blood creatinine increased	85 (25.4)	Very common	0	0		0	2 (0.6)
General disorder and administration site conditions							
Back pain	47 (14.1)	Very common	3 (0.9)	0	Uncommon	1 (0.3)	0
Fatigue	108 (32.3)	Very common	28 (8.4)	0	Common	3 (0.9)	5 (1.5)
Non-cardiac chest pain	50 (15.0)	Very common	7 (2.1)	0	Common	6 (1.8)	0
Oedema peripheral	173 (51.8)	Very common	29 (8.7)	0	Common	6 (1.8)	6 (1.8)
Pyrexia	48 (14.4)	Very common	2 (0.6)	0	Uncommon	4 (1.2)	1 (0.3)
Weight decreased	34 (10.2)	Very common	2 (0.6)	0	Uncommon	0	0
Frequency category is based on the following convention: very common (>=1/10); common (>=1/100 to <1/10); uncommon (>=1/1,000 to <1/100); rare (>=1/10,000 to <1/1,000); very rare (<1/10,000).							

The Applicant's Position:

Selection for candidates for adverse drug reactions (ADR) was performed by applying quantitative criteria (≥ 10% of all AEs and ≥ 3% of grade 3/4 events from Study A2201). In addition, selection for ADR candidates included all AEs leading to discontinuation, all AEs suspected by the investigator as drug-related, preferred terms captured by search terms in the case retrieval strategy (CRS) of the safety risk profile/management plan, all laboratory

abnormalities, all SAEs, all deaths (except those due to disease progression), and Novartis designated medical events.
Medical judgment on the inclusion/exclusion for an association with an AE was taken based on Bradford Hill criteria, biologic plausibility, and HA commitments to report or follow-up.

The FDA's Assessment:
AEs reported in >10% of patients in study A2201, along with Grade 3-4 incidence are presented in the table below. The most common adverse event reported with an incidence of ≥ 20% in patients treated with capmatinib were peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite.

Table 48: Adverse Reactions (≥ 10%) in Patients Who Received TABRECTA in study A2201

Adverse Reactions	TABRECTA (N = 334)	
	Grades 1 to 4 (%)	Grades 3 to 4[a] (%)
General disorders and administration-site conditions		
Peripheral edema[b]	52	9
Fatigue[c]	32	8
Non-cardiac chest pain[d]	15	2.1
Back pain	14	0.9
Pyrexia[e]	14	0.6
Weight decreased	10	0.6
Gastrointestinal disorders		
Nausea	44	2.7
Vomiting	28	2.4
Constipation	18	0.9
Diarrhea	18	0.3
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	24	7[a]
Cough	16	0.6
Metabolism and nutrition disorders		
Decreased appetite	21	0.9

[a] Only includes Grade 3 adverse reactions with exception of dyspnea. Grade 4 dyspnea was reported in 0.6% of patients.
[b] Peripheral edema includes peripheral swelling, peripheral edema, and fluid overload.
[c] Fatigue includes fatigue and asthenia.
[d] Non-cardiac chest pain includes chest discomfort, musculoskeletal chest pain, non-cardiac chest pain, and chest pain.
[e] Pyrexia includes pyrexia and body temperature increased.

Laboratory Findings

Biochemistry parameters

Data:

Table 49: Worst post-baseline clinical chemistry abnormalities based on CTC grades (Safety set)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Albumin - decrease	239 (71.6)	6 (1.8)	300 (71.6)	11 (2.6)	393 (72.6)	15 (2.8)
Creatinine - increase	223 (66.8)	1 (0.3)	270 (64.4)	1 (0.2)	324 (59.9)	2 (0.4)
Gamma glutamyl transferase – increase	156 (46.7)	29 (8.7)	190 (45.3)	36 (8.6)	261 (48.2)	62 (11.5)
Alkaline phosphatase - increase	152 (45.5)	2 (0.6)	196 (46.8)	4 (1.0)	273 (50.5)	16 (3.0)
Alanine aminotransferase – increase	128 (38.3)	26 (7.8)	158 (37.7)	31 (7.4)	211 (39.0)	35 (6.5)
Amylase - increase	120 (35.9)	14 (4.2)	144 (34.4)	23 (5.5)	161 (29.8)	23 (4.3)
Aspartate aminotransferase - increase	92 (27.5)	16 (4.8)	120 (28.6)	20 (4.8)	182 (33.6)	23 (4.3)
Lipase - increase	89 (26.6)	23 (6.9)	108 (25.8)	31 (7.4)	127 (23.5)	35 (6.5)
Sodium - decrease	84 (25.1)	20 (6.0)	108 (25.8)	25 (6.0)	153 (28.3)	36 (6.7)
Potassium – increase	74 (22.2)	10 (3.0)	87 (20.8)	10 (2.4)	104 (19.2)	12 (2.2)
Glucose - decrease	70 (21.0)	1 (0.3)	84 (20.0)	1 (0.2)	90 (16.6)	1 (0.2)
Magnesium - decrease	52 (15.6)	0	79 (18.9)	0	105 (19.4)	0
Potassium – decrease	31 (9.3)	6 (1.8)	44 (10.5)	9 (2.1)	56 (10.4)	10 (1.8)
Bilirubin - increase	26 (7.8)	3 (0.9)	31 (7.4)	3 (0.7)	64 (11.8)	8 (1.5)
Magnesium - increase	24 (7.2)	2 (0.6)	29 (6.9)	3 (0.7)	32 (5.9)	3 (0.6)
Sodium - increase	17 (5.1)	0	20 (4.8)	0	23 (4.3)	0

The Applicant's Position:

In Study A2201, clinical chemistry abnormalities were predominantly grade 1 or 2. The most common abnormal clinical chemistry laboratory parameters in any grades (occurring in ≥ 30% of subjects) were: albumin decrease (71.6%, 239 subjects), creatinine increase (66.8%, 223 subjects), GGT increase (46.7%, 156 subjects), ALP increase (45.5%, 152 subjects), ALT increase (38.3%, 128 subjects), and amylase increase (35.9%, 120 subjects).

The most common grade 3/4 clinical chemistry laboratory parameters (occurring in ≥ 5% of subjects) were: GGT increase (8.7%, 29 subjects), ALT increase (7.8%, 26 subjects), lipase increase (6.9%, 23 subjects), and sodium decrease (6.0%, 20 subjects) (Table 49).

Hematology
Data:

Table 50: Worst post-baseline hematology abnormalities based on CTC grades (Safety set)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N=334		N=419		N=541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hemoglobin- decrease	203 (60.8)	9 (2.7)	264 (63.0)	13 (3.1)	356 (65.8)	21 (3.9)
Lymphocytes - decrease	191 (57.2)	56 (16.8)	229 (54.7)	61 (14.6)	299 (55.3)	71 (13.1)
Leukocytes - decrease	80 (24.0)	3 (0.9)	98 (23.4)	5 (1.2)	119 (22.0)	6 (1.1)
Platelets - decrease	52 (15.6)	4 (1.2)	68 (16.2)	5 (1.2)	93 (17.2)	6 (1.1)
Neutrophils - decrease	48 (14.4)	8 (2.4)	50 (11.9)	8 (1.9)	57 (10.5)	9 (1.7)
Lymphocytes - increase	4 (1.2)	0	5 (1.2)	0	6 (1.1)	0

The Applicant's Position:

In Study A2201, hematological abnormalities post baseline were predominantly grade 1 or 2. The most frequently reported post-baseline hematological abnormalities of any grade (occurring in ≥ 30% of subjects) were: hemoglobin decrease (60.8%, 203 subjects) and lymphocytes decrease (57.2%, 191 subjects). All grade 3/4 hematological abnormalities were noted in ≤ 3% of the subjects, with only the exception of lymphocyte decrease which was noted in 16.8% (56 subjects) (Table 50).

The FDA's Assessment:
Laboratory abnormalities were analyzed using the laboratory datasets. The table below summarizes laboratory abnormalities worsening from baseline that occurred in ≥ 20% of patients in receiving capmatinib in study A2201.

Table 51: Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Who Received Capmatinib in study A2201

Laboratory Abnormalities	TABRECTA[a]	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
Hematology		
Decreased lymphocytes	44	14
Decreased hemoglobin	24	2.8
Decreased leukocytes	23	0.9
Chemistry		
Decreased albumin	68	1.8
Increased creatinine	62	0.3
Increased alanine aminotransferase	37	8
Increased alkaline phosphatase	32	0.3
Increased amylase	31	4.4
Increased gamma-glutamyltransferase	29	7
Increased lipase	26	7
Increased aspartate aminotransferase	25	4.9
Decreased sodium	23	6
Decreased phosphate	23	4.6
Increased potassium	23	3.1
Decreased glucose	21	0.3

[a]The denominator used to calculate the rate varied from 320 to 325 based on the number of patients with a baseline value and at least one post-treatment value.

Vital Signs

Data:

Table 52: Notable vital sign values (Safety set)

		Study A2201	All NSCLC subjects	All solid tumor subjects
		N=334	N=419	N=541
Vital sign	Category	n (%)	n (%)	n (%)
Systolic blood pressure	≥ 180 mmHg and increase ≥ 20 mmHg	5 (1.5)	6 (1.4)	7 (1.3)
	≤ 90 mmHg and decrease ≥ 20 mmHg	35 (10.5)	43 (10.3)	50 (9.2)
Diastolic blood pressure	≥ 105 mmHg and increase ≥ 15 mmHg	6 (1.8)	6 (1.4)	7 (1.3)
	≤ 50 mmHg and decrease ≥ 15 mmHg	24 (7.2)	30 (7.2)	38 (7.0)

Vital sign	Category	Study A2201 N=334 n (%)	All NSCLC subjects N=419 n (%)	All solid tumor subjects N=541 n (%)
Pulse rate	≥ 100 bpm and increase >25%	47 (14.1)	54 (12.9)	71 (13.1)
	≤ 50 bpm and decrease >25%	8 (2.4)	8 (1.9)	8 (1.5)
Weight	Increase ≥ 10%	51 (15.3)	60 (14.3)	66 (12.2)
	Decrease ≥ 10%	22 (6.6)	26 (6.2)	33 (6.1)
Temperature	≥ 39.1°C	13 (3.9)	14 (3.3)	15 (2.8)

The Applicant's Position:

In Study A2201 post-baseline, no clinically significant changes were noted for most of the vital signs (Table 52).

The FDA's Assessment:
FDA concurs with Novartis' analysis on vital signs values.

Electrocardiograms (ECGs)

Data:

Table 53: Notable ECG values (Safety set)

ECG parameter Notable criteria	Study A2201 N=334 n/m (%)	All NSCLC subjects N=419 n/m (%)	All solid tumor subjects N=541 n/m (%)
QTcF (ms)			
Increase >30 to ≤ 60 ms	11/323 (3.4)	14/400 (3.5)	18/510 (3.5)
Increase >60 ms	1/323 (0.3)	1/400 (0.3)	1/510 (0.2)
New >450 to ≤ 480 ms	4/313 (1.3)	6/386 (1.6)	9/493 (1.8)
New >480 to ≤ 500 ms	3/323 (0.9)	4/399 (1.0)	4/508 (0.8)
New >500 ms	0/323 (0)	0/400 (0)	0/510 (0)
QTcB (ms)			
Increase >30 to ≤ 60 ms	20/323 (6.2)	25/376 (6.6)	28/431 (6.5)
Increase >60 ms	3/323 (0.9)	3/376 (0.8)	3/431 (0.7)
New >450 to ≤ 480 ms	35/284 (12.3)	40/328 (12.2)	48/376 (12.8)

ECG parameter Notable criteria	Study A2201 N=334 n/m (%)	All NSCLC subjects N=419 n/m (%)	All solid tumor subjects N=541 n/m (%)
New >480 to ≤ 500 ms	5/322 (1.6)	7/373 (1.9)	7/427 (1.6)
New >500 ms	2/323 (0.6)	3/376 (0.8)	3/431 (0.7)
QT (ms)			
Increase >30 to ≤ 60 ms	76/323 (23.5)	91/400 (22.8)	118/510 (23.1)
Increase >60 ms	17/323 (5.3)	20/400 (5.0)	27/510 (5.3)
New >450 to ≤ 480ms	10/314 (3.2)	12/388 (3.1)	16/495 (3.2)
New >480 to ≤ 500 ms	3/322 (0.9)	3/398 (0.8)	3/506 (0.6)
New >500 ms	0/322 (0)	0/399 (0)	0/509 (0)
PR (ms)			
Increase >25% and PR >200 ms	1/291 (0.3)	1/366 (0.3)	1/467 (0.2)
New PR >200 ms	17/291 (5.8)	21/366 (5.7)	22/467 (4.7)
QRS (ms)			
Increase >25% and QRS >120 ms	2/303 (0.7)	2/375 (0.5)	2/482 (0.4)
New QRS > 120 ms	3/303 (1.0)	4/375 (1.1)	5/482 (1.0)
Heart rate (HR; beats per minute (bpm))			
Increase >25% and HR >100 bpm	20/289 (6.9)	23/356 (6.5)	31/456 (6.8)
Decrease >25% and HR <50 bpm	4/319 (1.3)	4/395 (1.0)	4/505 (0.8)

n: Number of subjects at risk whose worst post-baseline value meets the criterion.
m: Number of subjects at risk.

The Applicant's Position:

In Study A2201, capmatinib did not prolong the QTc interval to any clinically relevant extent. No subject experienced a new post baseline QTcF value >500 ms. QTcF increases from baseline > 60 ms were noted in 1 subject (0.3%).In this subject, there was significant variability in the QT measurements between screening and the designated pre-dose baseline on Day 1. The highest post-dose value was similar to the off-treatment ECG collected at screening. Three subjects had QTcF increase from baseline of > 480 ms to ≤500 ms . None of the QTcF values > 480 ms was associated with cardiac clinical symptoms or arrhythmias (Table 53).
Taking into consideration a lack of nonclinical evidence for QTc interval prolongation risk as well as clinical data demonstrating that capmatinib does not prolong the QT interval to any clinically relevant extent, a potential clinical risk of QT prolongation does not need to be communicated as a warning in the labeling (Table 53).

The FDA's Assessment:
FDA concurs with Novartis' analysis.

QT

Data:

Table 54: Incidence of QTc interval prolongation (Safety set)

	Study A2201	All NSCLC subjects	All solid tumor subjects
	N=334	N=419	N=541
	n (%)	n (%)	n (%)
Number of subjects with at least one event (95% CI)	10 (3.0) (1.4, 5.4)	12 (2.9) (1.5, 5.0)	14 (2.6) (1.4, 4.3)
Exposure-adjusted overall incidence, n (IR per 100 STM*)	10 (0.5)	12 (0.5)	14 (0.5)
Maximum grade			
Grade 3 AEs	1 (0.3)	2 (0.5)	2 (0.4)
Grade 4 AEs	2 (0.6)	3 (0.7)	3 (0.6)
Grade 3/4 AEs	3 (0.9)	5 (1.2)	5 (0.9)
Treatment-related AEs	3 (0.9)	3 (0.7)	3 (0.6)
SAEs	2 (0.6)	3 (0.7)	4 (0.7)
Action taken			
Drug interrupted	0	0	1 (0.2)
Dose not changed	9 (2.7)	9 (2.1)	10 (1.8)
Not applicable	1 (0.3)	3 (0.7)	3 (0.6)
*Incidence rate per 100 subject-months			

The Applicant's Position:

No dedicated QT studies were conducted for capmatinib. Exposure-QTc analysis was conducted using pooled time-matched PK and ECG data from Study A2201 and Study A2108. Based on the linear mixed-effect model, a flat slope was identified with QTcF increase of 0.62 ms (95% CI: 0.338, 0.909) for every 1000 ng/mL capmatinib plasma concentration increase. At the mean steady state Cmax of 5447.9 ng/mL following 400 mg b.i.d. capmatinib administration, the estimated mean QTcF change from baseline was 1.33 ms (90% CI; 0.090, 2.575). This effect is not clinically relevant as the upper 90% CI of 2.575 ms is well below the regulatory threshold of 10 ms.

The aggregated PTs used to identify this AESI were based on the standardized MedDRA Query (SMQ-Torsade de pointes/QT prolongation), and PTs using MedDRA version 22.0. There was no nonclinical evidence of QTc interval prolongation.

In Study A2201**,** 10 subjects (3.0%) had QTc interval prolongation grouped AESIs; Of these, 3 subjects (0.9%) reported grade 3/4 events. Adverse events (any grade) that were suspected to be study drug-related were reported in 3 subjects (0.9%); QTc prolongation in 2 subjects (0.6%) and cardiac arrest in one subject (0.3%). However, there was no discontinuation of treatment due to these AEs. Serious AEs of cardiac arrest were reported in 2 subjects, both of which resulted in death (Table 54).

The FDA's Assessment:
FDA concurs with Novartis' analysis regarding the incidence of QTc prolongation.

Immunogenicity

The Applicant's Position:

Not applicable as this was not assessed nor expected.

The FDA's Assessment:

FDA concurs with Novartis' statement.

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse events of special interest

Data:

Table 55: Overview of adverse events of special interest (Safety set)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N = 334		N = 419		N = 541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Safety topic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hepatotoxicity	94 (28.1)	32 (9.6)	121 (28.9)	43 (10.3)	166 (30.7)	57 (10.5)
Renal dysfunction	89 (26.6)	1 (0.3)	110 (26.3)	1 (0.2)	128 (23.7)	2 (0.4)
CNS toxicity	62 (18.6)	3 (0.9)	78 (18.6)	3 (0.7)	91 (16.8)	3 (0.6)
Pancreatitis	41 (12.3)	26 (7.8)	58 (13.8)	35 (8.4)	64 (11.8)	39 (7.2)
ILD/pneumonitis	15 (4.5)	6 (1.8)	15 (3.6)	6 (1.4)	15 (2.8)	6 (1.1)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N = 334		N = 419		N = 541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Safety topic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
QTc interval prolongation	10 (3.0)	3 (0.9)	12 (2.9)	5 (1.2)	14 (2.6)	5 (0.9)
Photosensitivity	1 (0.3)	0	1 (0.2)	0	1 (0.2)	0
Teratogenicity	0	0	0	0	0	0
DDI with strong CYP3A4 inducers	0	0	0	0	0	0

CNS = central nervous system; DDI = drug-drug interactions; ILD =interstitial lung disease
MedDRA version 22.0, CTCAE version 4.03, Case Retrieval Strategy version released 29-Jul-2019.

The Applicant's Position:

An AESI is a grouping of AEs that are of particular scientific or medical concern specific to capmatinib or this class of antineoplastic medication. The AESI selected for capmatinib are provided in Table 55. Details of each AESI are described below.

Interstitial lung disease/pneumonitis
In Study A2201, 15 of 334 subjects (4.5%) experienced ILD/pneumonitis: 12 subjects (3.6%) with pneumonitis and 3 (0.9%) with ILD. Most of these subjects (10 out of 15) had prior treatment with IO agents (nivolumab and pembrolizumab) for the treatment of their lung cancer and/or radiotherapy to the lung fields for treatment of their lung cancer as confounding factors and/or had lung progressive disease at the onset of ILD/pneumonitis. Eight subjects (2.4%) discontinued study treatment due to these AEs. One fatal event of pneumonitis was reported.

Hepatotoxicity
In Study A2201, 94 of 334 subjects (28.1%) reported hepatotoxicity-grouped AESIs. Of these, 9.6% (32 subjects) were reported as grade ¾ and 1.5% (5 subjects) were having ≥ 1 SAE. The most common (all grade) PTs (≥ 5% of the subjects) were: ALT increased (12.6%; 42 subjects), AST increased (8.7%; 29 subjects), hypoalbuminemia (8.7%; 29 subjects), GGT increased (7.2%; 24 subjects), and blood ALP increased (5.7%; 19 subjects). Transaminase elevations generally occurred within approximately the first 12 weeks of treatment. Discontinuation of treatment due to hepatotoxicity-grouped AESI was low (1.8%; 6 subjects). Fatal outcome was reported for the SAE hepatitis and was confounded by multiple factors (this subject had liver metastasis at the screening visit and a medical history of cholangitis). The Investigator assessed the fatal case of hepatitis as also related to concomitant medication of acitretin (Soriatane).

Based upon the clinical and laboratory data review, no subjects were confirmed to meet the criteria for DILI (concurrent elevations in ALT/AST > 3 x ULN and total bilirubin > 2 x ULN with ALP < 2 x ULN and no confounding factors with clinical evidence of DILI) either in Study A2201 nor in the pooled datasets of All subjects with NSCLC or All subjects with solid tumors.

With regards to liver function tests, in Study A2201, increases in LFTs post-baseline (of any grade) were observed in: 38.3% (128 subjects; ALT increase), 45.5% (152 subjects; ALP increase), and 27.5% (92 subjects; AST increase). However, the grade 3/4 increases were observed in low number of subjects (≤ 9% of subjects) (Table 49). 1 subject had levels of transaminases, total bilirubin, and ALP consistent with potential clinical Hy's Law criteria. Upon medical review, this case did not meet the clinical Hy's Law criteria. Therefore, no confirmed cases of DILI/Hy's Law were observed in Study A2201 or in the pooled safety databases.

Renal dysfunction
In Study A2201, 26.6% (89 subjects) had renal dysfunction-grouped AESIs, with 20.4% (68 subjects) with study drug related events. With the exception of 1 subject (0.3%) with grade 3 renal dysfunction, all other renal AESIs were either grade 1 or 2. The number of subjects requiring drug withdrawal/discontinuation was low (0.6%; 2 subjects). None of the renal dysfunction-grouped events resulted in death.

CNS toxicity
In Study A2201, 18.6% (62 subjects) had CNS toxicity-grouped AESIs, including 4.5% (15 subjects) with study drug related events. None of these subjects had a grade 4 event and 0.9% (3 subjects) had grade 3 events. The most frequently noted CNS toxicity-grouped AESIs (occurring in ≥ 1% of subjects) were: dizziness (8.7%; 29 subjects), vertigo (4.5%; 15 subjects), dysphonia (2.1%; 7 subjects), seizure (1.5%; 5 subjects), and tremor (1.2%; 4 subjects); all other AEs were noted in either 1 or 2 subjects. Six subjects (1.8%) had CNS toxicity-grouped SAEs: seizure (3 subjects), epilepsy (2 subjects), and vertigo (1 subject). All the aforementioned subjects with CNS toxicity-grouped SAEs had brain metastasis at baseline (with the exception of one Subject who had gamma knife irradiation of brain metastasis 814 days prior to the study entry), and the investigator did not suspect any relationship between these SAEs and the study drug. None of these subjects discontinued study treatment due to these CNS toxicity grouped events and none of the events was fatal.

Pancreatitis
In Study A2201, 12.3% (41 subjects) had pancreatitis-grouped AESIs, including 11.4% (38 subjects) who had study drug related events. In 0.6% (2 subjects), these events were considered as SAEs (amylase increased and acute pancreatitis each in 1 subject). Pancreatitis-grouped events were of grade 3/4 severity for 7.8% (26 subjects). With the exception of the single case of acute pancreatitis, all other pancreatitis-grouped events (any grade) were elevations in pancreatic enzymes (amylase increased in 8.7% (29 subjects) and/or lipase

increased in 7.8% (26 subjects) (Table 49). The number of subjects discontinuing the study treatment due to pancreatitis-grouped events was low (0.6%; 2 subjects). None of the pancreatic-grouped AESIs were fatal.

Photosensitivity
Nonclinical studies indicated a photosensitive effect with capmatinib. However, only 1 subject (0.3%) reported grade 1 photosensitivity in Study A2201 which was considered as study drug related by the investigator. This event did not require any dose change and the subject did not discontinue study drug. The subject had psoriasis at baseline, which was a confounding factor.

Teratogenicity
The observed teratogenicity in animal species is consistent with the mechanism of action by MET inhibition. Capmatinib should be considered potentially fetotoxic and teratogenic to humans. However, there was no case of pregnancy in any clinical study with capmatinib, including Study A2201.

DDI with strong CYP3A4 inducers
One subject had received concomitant medication of phenytoin during the course of A2201 study. However, there was no sign of lack of efficacy due to a drug-drug interaction with capmatinib.

QTc Interval prolongation
Details of QTc interval prolongation are described above and data are presented in Table 54.

Clinical implications of the AESIs:

Clinical implications of ILD/pneumonitis: There were no adverse lung findings in nonclinical studies. However, taking into consideration the class effect of ILD/pneumonitis for Tyrosine kinase inhibitors (TKIs), the clinically significant implication of ILD/pneumonitis events as well as the importance of monitoring patients and intervening in suspected cases of ILD/pneumonitis, a potential risk of ILD/pneumonitis as well as guidance on actions to be taken will be communicated as a warning in the labeling.

Clinical implication of hepatoxicity: Taking into consideration both nonclinical and clinical evidence of changes in serum chemistry liver enzymes, which were severe (grade 3/4) in a number of cases, as well as the ability to mitigate potentially clinically significant implications of elevated liver enzymes through regular liver function test monitoring and dose modifications, a potential risk of hepatic effects as well as guidance on actions to be taken will be communicated as a warning in the labeling.

Clinical implication of renal dysfunction: Mild/moderate (grade 1/2) blood creatinine increases reported in subjects treated with capmatinib account for the majority of renal-dysfunction-

related events. The reversible inhibition of active renal transporters MATE1 and MATE2K which are involved in creatinine clearance is expected to cause blood creatinine increases. Taking into consideration the lack of nonclinical evidence of renal function impairment, the mechanistic causality, the absence of clinically severe (grade 3/4) creatinine increase, and other renal dysfunction-related events being extremely uncommon (0.3%), a potential clinical risk of renal dysfunction does not need to be communicated as a warning in the labeling.

Clinical implication of CNS toxicity: Taking into consideration the presence of underlying brain metastases in the clinically significant CNS-grouped events reported by subjects treated with capmatinib, a potential clinical risk of CNS toxicity does not need to be communicated as a warning in the labeling.

Clinical implications of pancreatitis: Taking into consideration the nature of the majority of the reported pancreatitis-grouped events which were mainly asymptomatic and reversible pancreatic enzyme elevations, a potential clinical risk of pancreatitis does not need to be communicated as a warning in the labeling.

Clinical implications of photosensitivity: Taking into consideration the nonclinical evidence indicating a photosensitive effect of capmatinib, limited clinical data as well as the precautionary measures implemented in the Study A2201 to minimize exposure to sunlight and ultraviolet (UV) light, a potential risk of photosensitivity and guidance on the use of precautionary measures will be communicated as a warning in the labeling.

Clinical implications of teratogenicity: Taking into consideration the nonclinical evidence of a fetotoxic and teratogenic effect of capmatinib and the lack of clinical data related to pregnancy, a potential risk of embryo-fetal toxicity in humans and associated contraception recommendations will be communicated as a warning in the labeling.

Clinical implications of DDI with strong CYP3A inducers: In healthy subjects, co-administration of a single 400 mg capmatinib dose with the strong CYP3A inducer rifampicin (600 mg once daily for 9 days) decreased capmatinib AUCinf by 67% and Cmax by 56% compared to administration of capmatinib alone. Concomitant use of capmatinib 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 concomitant medication with no or minimal potential to induce CYP3A should be considered. These recommendations will be communicated in the drug interactions section of the labeling.

Clinical implications of QTc interval prolongation: Taking into consideration a lack of nonclinical evidence for QTc interval prolongation risk as well as clinical data demonstrating that capmatinib does not prolong the QT interval to any clinically relevant extent, a potential clinical risk of QT prolongation does not need to be communicated as a warning in the labeling.

The FDA's Assessment:

FDA agrees with the AESI analysis and assessment of capmatinib by Novartis. An overview of the adverse events of special interest is provided below in the table. The highlighted safety topics within the table were deemed appropriate to be included in the Warnings and Precaution section of the label. The remaining safety topics were not included in the Warnings and Precaution (section 5) of the label due to the low incidence in either all grades or Grade 3-4.

Table 56: Overview of Adverse Events of Special Interest (AESI)

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N = 334		N = 419		N = 541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Safety topic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
ILD/pneumonitis	4.5	1.8	3.6	1.4	2.8	1.1
Hepatotoxicity	28	10	29	10	31	11
Photosensitivity	0.3	0	0.2	0	0.2	0
Renal dysfunction	27	0.3	26	0.2	24	0.4
CNS toxicity	19	0.9	19	0.7	17	0.6
Pancreatitis	12	8	14	8	12	7
QTc interval prolongation	3.0	0.9	2.9	1.2	2.6	0.9

Interstitial lung disease/pneumonitis

ILD/pneumonitis occurred in 4.5% of patients treated with capmatinib in study A2201, with 1.8% of patients experiencing Grade 3 ILD/pneumonitis and one patient experiencing death (0.3%). Eight patients (2.4%) discontinued capmatinib due to ILD/pneumonitis. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 1.4 months (range: 0.2 months to 1.2 years 4.8 months).

Hepatotoxicity

Increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in 13% of patients treated with capmatinib in study A2201. Grade 3 or 4 increased ALT/AST occurred in 6% of patients and three patients (0.9%) discontinued capmatinib due to increased ALT/AST. The median time-to-onset of Grade 3 or higher ALT/AST elevations was 1.4 months (range: 0.5 to 4.1 months).

Photosensitivity

While there was one Grade 1 case of photosensitivity in study A2201, based on findings from

animal studies, there is a potential risk of photosensitivity reactions in capmatinib. In study A2201, patients were recommended to wear sunscreen and protective clothing in order to minimize exposure to ultra-violet light.

CNS toxicity
An analysis of grouped preferred terms for cognitive effects, peripheral neuropathy, CNS toxicity, and cognitive effects was conducted to reveal that these incidences did not meet the level that warrants inclusion in the Warnings and Precaution section of the capmatinib label.

Table 57: Overview of CNS-related AEs

	Study A2201		All NSCLC subjects		All solid tumor subjects	
	N = 334		N = 419		N = 541	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Safety topic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cognitive Effects	15	1.5	17	1.4	15	1.3
Peripheral Neuropathy	8	1.2	9	1.2	9	0.9
CNS toxicity	17	0.9	17	0.7	15	0.6
Mood Effects	8	0	8	0.2	8	0.4

The PT used to identify cases of cognitive effects are amnesia, cognitive disorder, dementia, disturbance in attention, memory impairment, mental impairment, attention deficit/hyperactivity disorder, confusional state, delirium, disorientation, reading disorder, dizziness, vertigo, dizziness postural, amnesia, aphasia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, visual hallucination, memory impairment, mental disorder, and mental status changes.

The PT used to identify cases of peripheral neuropathy are burning sensation, carpal tunnel syndrome, dysesthesia, formication, gait disturbance, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral sensory neuropathy, sensory disturbance, paresthesia, hyperesthesia, hypoesthesia, dysesthesia, oral hypoesthesia, palmar-plantar erythrodysesthesia, oral paresthesia, and genital hypoesthesia.

The PT used to identify CNS toxicity are dizziness, vertigo, dysphonia, seizure, tremor, cns toxicity, convulsions, vestibular disorders, parkinson-like events, and epilepsy.

The PT used to identify mood effects are affective disorder, affect lability, aggression, agitation, anxiety, depressed mood, depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress, suicidal ideation, anxiety, affect lability, affective disorder,

agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, and psychomotor retardation.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Patient-reported outcomes have been discussed in the efficacy section of this report (Section 8.1.2).

The FDA's Assessment:
Refer to PRO discussion in section 8.1.2.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Subgroup analyses were conducted to identify potential safety issues that were limited to a subgroup of subjects, or safety issues that were more commonly observed in a subgroup of subjects.
Overall, the various subgroup analyses demonstrated a pattern of events that was generally consistent with that reported for the overall population in Study A2201, in All NSCLC subjects and in All solid tumor subjects.
By age: In Study A2201, there were 140 subjects, 134 subjects, 47 subjects, and 7 subjects in the <65 years, ≥ 65 to 75 years, and ≥ 75 to <85 years age categories, respectively, who experienced at least one AE. As there were only 7 subjects in the ≥ 85-year-old category, subjects from this category were excluded from the comparison of AEs or AESIs across age groups.
In Study A2201, AEs with incidences of ≥ 20% and with differences of 10% across any of the age categories are presented below (in the sequence of <65 years vs. ≥ 65 to 75 years vs. ≥ 75 to <85 years, respectively:

- Vomiting: 29.4% (42 subjects) vs. 31.4% (43 subjects) vs. 19.1% (9 subjects)
- Peripheral edema: 43.4% (62 subjects) vs. 51.1% (70 subjects) vs. 66.0% (31 subjects)
- Increased blood creatinine: 17.5% (25 subjects) vs. 28.5% (39 subjects) vs. 42.6% (20 subjects).

By gender: There were more male subjects (59.0%, 197 subjects) compared to females (41.0%, 137 subjects) in Study A2201. The AEs that were observed with incidences of ≥ 20% and with a difference of 10% across both subgroups were peripheral edema (56.2% in females and 45.2%

in males) and nausea (50.4% in females and 39.6% in males). The incidence of all other AEs across both genders was similar.

By race: In Study A2201, the predominant race was Caucasian (248 subjects, 74.3%) followed by Asian (81 subjects, 24.3%). Due to the limited subject number in the "others" category (5 subjects, 1.5%), this was not included in the below comparison.
In Study A2201, the AEs with incidences of ≥ 20% and with differences of 10% across the race categories are presented below in the sequence of Caucasian vs. Asian, respectively.

- Peripheral edema: 55.6% (138 subjects) vs. 32.1% (26 subjects)
- Pyrexia: 11.3% (28 subjects) vs. 22.2% (18 subjects)
- Increased blood creatinine: 21.8% (54 subjects) vs. 37.0% (30 subjects)
- Decreased appetite: 17.7% (44 subjects) vs. 30.9% (25 subjects)
- Dyspnea: 29.0% (72 subjects) vs. 9.9% (8 subjects).

By ECOG status: In Study A2201, as per protocol, 29.3% (98 subjects) and 70.4% (235 subjects) had ECOG-PS of 0 and 1, respectively, at baseline (only 1 subject (0.3%) had an ECOG-PS score of 2, which was reported as a protocol deviation). With the exception of fatigue (29.6% vs. 18.2% in subjects with ECOG status of 0 and ≥ 1, respectively), the incidences of AEs were similar (i.e. differences were < 10%) across ECOG/WHO status of 0 and ≥ 1.

By geographic region: In Study A2201, the AEs with incidences of ≥ 20% in any geographic region and also with a difference of 10% across any geographic region are presented below in the sequence of Asia/Pacific (N=76 subjects) vs. Europe/Middle East (N=220 subjects) vs. Americas (N=38 subjects), respectively.

- Vomiting: 32.9% (25 subjects) vs. 27.7% (61 subjects) vs. 21.1% (8 subjects)
- Constipation: 25.0% (19 subjects) vs. 16.4% (36 subjects) vs. 13.2% (5 subjects)
- Peripheral edema: 34.2% (26 subjects) vs. 55.9% (123 subjects) vs. 44.7% (17 subjects)
- Fatigue: 22.4% (17 subjects) vs. 18.2% (40 subjects) vs. 39.5% (15 subjects)
- Pyrexia: 22.4% (17 subjects) vs. 11.4% (25 subjects) vs. 13.2% (5 subjects)
- Increased blood creatinine: 39.5% (30 subjects) vs. 21.8% (48 subjects) vs. 18.4% (7 subjects)
- Decreased appetite: 28.9% (22 subjects) vs. 16.4% (36 subjects) vs. 28.9% (11 subjects)
- Dyspnea: 9.2% (7 subjects) vs. 30.5% (67 subjects) vs. 18.4% (7 subjects)
- Nausea: 47.4% (36 subjects) vs. 43.2% (95 subjects) vs. 42.1% (16 subjects).

By hepatic impairment: 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. Cmax was decreased by approximately 28% and 17% in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function, while Cmax was similar (differed by 2%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

By renal impairment: 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. Capmatinib has not been studied in patients with severe renal impairment.

The FDA's Assessment:
FDA verified and agrees with the age and gender analysis above.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees with Novartis that specific safety studies are not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:
Carcinogenicity studies have not been conducted with capmatinib.

The FDA's Assessment:
FDA agrees with Novartis statement.

Human Reproduction and Pregnancy

The Applicant's Position:

Studies on embryofetal development in rats and rabbits indicated that capmatinib is fetotoxic and teratogenic in both species. This effect is consistent with the mechanism of action of MET inhibition. Capmatinib should be considered potentially fetotoxic and teratogenic to humans.

Pregnant women should be advised of the potential risk to the fetus if capmatinib is used during pregnancy or if the patient becomes pregnant while taking capmatinib. Due to the risk of teratogenicity, pregnancy status in females of reproductive potential should be verified before starting treatment.

There are no data available from animal studies or humans on the transfer of capmatinib into breast milk, the effects of capmatinib on a breastfed child, or the effects of capmatinib on milk production. Due to lack of nonclinical or clinical data and the potential for serious adverse drug reactions in breastfed children, breastfeeding is not recommended during treatment with capmatinib and for at least 7 days after last dose.

The FDA's Assessment:
FDA agrees with Novartis position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable.

The FDA's Assessment:
FDA agrees with Novartis position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Position:

No information about overdose has been generated in support of this application. 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. No information about withdrawal and rebound has been generated in support of this application.

The FDA's Assessment:
FDA agrees with Novartis position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable as capmatinib is not yet marketed in any region.

The FDA's Assessment:
FDA agrees with Novartis position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety data of capmatinib are adequate in the context of a rare disease with high unmet need. Published information on the safety of capmatinib (and MET inhibitors in general) is evaluated on an ongoing basis with respect to both nonclinical findings and data from ongoing clinical studies. Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected AEs.

The FDA's Assessment:
The review teams determined that a REMS is not required to ensure safe and effective use of capmatinib. Capmatinib will be prescribed by oncologists who are trained on how to monitor, diagnose, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Treatment with capmatinib is generally safe and tolerable in the intended target population, with a low rate of permanent discontinuation due to treatment-related AEs. In the context of the significant clinical benefit observed for this population with limited effective therapeutic options, the overall safety profile is acceptable, and the benefit-risk profile is favorable.

Key safety topics

Potentially important side effects have been identified, these include ILD/pneumonitis, hepatic effects, teratogenicity, and photosensitivity. The clinical impact of these events can be mitigated by appropriate management as described in the proposed label.

Deaths were attributable to disease progression in 43 of the 53 cases in Study A2201, of the remaining 10 deaths, only 1 (a case of pneumonitis) was confirmed to be treatment-related following review by Novartis.
While SAEs were reported in 50.6% of patients, the incidence of specific individual SAEs was low.
The most common treatment-related AEs were peripheral edema, nausea, vomiting, increased blood creatinine, decreased appetite, diarrhea and fatigue. The majority of events were grade 1 or 2 and were effectively managed by dose adjustments or interruptions.

Unanswered safety questions
Data relative to rare safety signals are currently limited and missing information includes safety in long-term use. No data are available for the use of capmatinib in pregnant women, capmatinib should therefore not be administered to pregnant women unless the potential benefit outweighs the risk to the fetus.

Conclusions
In conclusion, capmatinib has an acceptable and manageable safety profile for subjects with with locally advanced or metastatic NSCLC. The AEs reported are well characterized and manageable with dose interruptions and/or dose modifications, and are generally reversible. The safety in the intended patient population is consistent with the safety profile of capmatinib derived from pooled data across several studies, no new safety risks were identified during the conduct of Study A2201.

The FDA's Assessment:
The above safety assessment incorporates data from multiple trials and is therefore is considered integrated.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:
Data were analyzed according to the plan pre-specified in the statistical analysis plan. There were no major statistical issues in the application. The indication of capmatinib for treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping as detected by an FDA-approved test is mainly supported by non-randomized cohorts with 69 previously treated patients in cohort 4 and 28 treatment-naïve patients in cohort 5B in Study A2201. Estimated effect sizes should be interpreted with caution because relatively small cohorts, such as cohort 5B, may yield a non-robust point estimate of the true underlying

treatment effect.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the data in Study A2201, patients with MET exon-14 skipping NSCLC (28 patients in the treatment-naïve setting and 69 patients in the previously treated setting), capmatinib demonstrates a clinically meaningful ORR and duration of response The estimated ORR as assessed by BICR in the first line setting was 68% (95% CI: 48, 84) and in the pretreated setting BICR ORR was 41% (95% CI: 29, 53). The median duration of response for the treatment-naïve population is 12.6 (5.5, 25.3) months and 9.7 (5.5, 13) months in the previously treated population.

To obtain additional efficacy data to confirm the clinical benefit of capmatinib in treatment-naïve patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping mutations, FDA recommends that Novartis submit reports, including datasets, that further characterize the clinical benefit of capmatinib in at least 60 patients after all responders have been followed for at least 12 months from the date of initial response (or until disease progression, whichever comes first). For the treatment of patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping and who have previously received platinum-based chemotherapy, FDA recommends that Novartis submit reports including data for 85 patients with updated duration of response after all responders have been followed for at least 6 months along with additional supportive data (i.e. updated ORR in the 2nd line treatment setting patients in cohort 6) to provide a more precise estimation of an update on the BICR-assessed overall response rate (ORR) and duration of response (DOR). These patient populations will include the 28 treatment-naïve and 69 previously treated patients comprising the primary efficacy analysis population for this review.

The safety data set included 541 patients with solid tumors who were treated with capmatinib at the recommended dose, and this includes 334 patients from the registration study A2201. The most common adverse events associated with capmatinib treatment were peripheral edema, nausea, fatigue/asthenia, vomiting, dyspnea, and decreased appetite. Most adverse events were grade 1 or 2 and managed by study drug reduction and/or interruption, and discontinuation of study drug due to adverse events were infrequent. Serious adverse reactions occurred in 51% of patients who received capmatinib however the serious risks are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of capmatinib product labeling. Most discontinuations were attributed to disease progression from the underlying cancer and the rate of permanent discontinuation of capmatinib due to adverse events was 16%. The adverse reaction profile is acceptable when assessed in the context of clinical benefit observed and the life-threatening nature of metastatic NSCLC.

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for accelerated approval and provides preliminary evidence of the effectiveness of capmatinib as a single agent in patients with MET exon 14 skipping mutation in the treatment-naïve and previously treated settings. The reviewers recommend granting accelerated approval of capmatinib for the following indication: "TABRECTA is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test."

X	X
Primary Statistical Reviewer Anup Amatya, Ph.D.	Statistical Team Leader Mallorie Fiero, Ph.D.
X	X
Primary Clinical Reviewer Luckson Mathieu, M.D.	Clinical Team Leader Erin Larkins, M.D.

9 Advisory Committee Meeting and Other External Consultations

<u>The FDA's Assessment:</u>
The division did not refer this efficacy supplement to an advisory committee because the application did not raise significant public health questions on the role of capmatinib in the proposed indication. The application also did not raise significant safety or efficacy issues.

10 Pediatrics

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA granted capmatinib orphan designation for treatment of NSCLC with MET genomic tumor aberrations in March 15, 2019. Because capmatinib has orphan drug designation for NSCLC it is exempt from the PREA requirements and no pediatric studies have been conducted in NSCLC. For approved drugs or biological products for which orphan designation has been granted are exempt from the PREA section 505B(a)(a)(A) requirement to conduct a pediatric assessment.

11 Labeling Recommendations

The table below summarizes changes to the proposed prescribing information for capmatinib. See the final approved prescribing information for TABRECTA (capmatinib) accompanying the approval letter for final labeling.

Table 58: Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Indications and Usage	...	Added age groups based on recommendations found in the Indications and Usage Section of Labeling guidance. Added the statement, this indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Dosage and Administration, Recommended Dosage Modifications for Adverse Reactions	...	Modified table 1 (recommended dose reductions) to omit (b) (4) (b) (4) Modified table 2 (recommended dosage modifications) for adverse reactions to create a three-column table: adverse reaction, severity and dosage modification to improve readability.
Warnings and Precautions, Interstitial Lung Disease/	...	Added number of patients who required permanent discontinuation for this adverse reaction and deleted

Pneumonitis		information [redacted].
Warnings and Precautions, Photosensitivity	Included a precaution based on animal data.	Modified subsection title to indicate that these reactions were not observed in clinical trials. Added a description of the risk mitigation strategies used in the clinical trial GEOMETRY MONO-1.
Adverse Reactions	Included two tables to describe adverse reactions and laboratory abnormalities.	Modified tables to include grades 1-4 and grades 3-4 and list categories in decreasing order. Included a description of fatal adverse reactions. Omitted the [redacted]
Drug Interactions	Included information on CYP3A inhibitors, CYP3A inducers, [redacted] CYP1A2 substrates and P-gp and BCRP substrates.	Omitted information on [redacted].
Use in Specific Populations, Pregnancy	...	Modified to provide an integrated risk summary and include animal doses expressed in terms of exposure equivalents as specified in 21 CFR 201.57 (c)(9)(i)(B) (2).
Use in Specific Populations, Renal Impairment	[redacted]	Modified to state that capamatinb has not been studied in patients with severe renal impairment.
[redacted]	...	[redacted]
Description	...	Modified pharmacologic or

		therapeutic class to the established pharmacologic class listed in the Highlights. Added other important chemical or physical information based on 21 CFR 201.57 (c)(12)(ii).
Clinical Pharmacology, Pharmacodynamics	(b) (4)	Revised to state that the exposure-response relationship and time course of pharmacodynamics in humans is unknown.
Clinical Pharmacology, Pharmacokinetics	Included description of inactive metabolites (b) (4)	Removed (b) (4) as this subsection must describe clinically significant pharmacokinetics of the drugs or active metabolites (21 CFR 201.57 (c)(13)(i)(C) and 21 CFR 201.56(a)(1)).
Clinical Studies	…	(b) (4) Added a description of the centrally confirmed results of the clinical trial assay used to measure MET exon 14 skipping. (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of capmatinib for the indicated population. Recommendations for the safe and effective use of capmatinib are made in labeling and a Patient package insert. There are no additional risk management strategies required beyond the recommended labeling. Although capmatinib can cause severe/serious toxicity, it will be prescribed by oncologists who, by training, understand how to monitor and manage such serious toxicities.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
Novartis has agreed to the following postmarketing requirement (PMR):

Clinical PMR:

Submit the final reports including datasets from clinical studies to confirm and further characterize the clinical benefit of capmatinib for the treatment of patients with Non-Small Cell Lung Cancer (NSCLC) whose tumors have a mutation that leads to MET exon 14 skipping who are treatment-naïve and who have previously received platinum-based chemotherapy, by providing a more precise estimation of the blinded independent central review-assessed overall response rate and duration of response. This report will contain data from NSCLC patients whose tumors have a mutation that leads to MET exon 14 skipping; data from at least 60 patients who are treatment naïve, after all responders have been followed for at least 12 months from the date of initial response (or until disease progression, whichever comes first); and from at least 85 patients who have been treated with platinum-based therapy, after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first).

Final Protocol Submission:	03/2019 (completed)
Trial Completion:	04/2021
Final Report Submission:	02/2022

14 Division Director (DHOT) (NME ONLY)

X

John Leighton, Ph.D.
Director, Division of Hematology, Oncology, and Toxicology

15 Division Director (OCP)

X

Nam Atiqur Rahman, Ph.D.
Director, Office of Clinical Pharmacology

16 Division Director (OB)

X

Shenghui Tang, Ph.D.
Director, Office of Biometrics

17 Division Director (Clinical)

X

Harpreet Singh, M.D.
Acting Director, Division of Oncology 2

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Marc R. Theoret, M.D.
Acting Deputy Director, Office of Oncologic Diseases

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

The Applicant provided financial disclosure for all clinical investigators involved in the studies included in this submission in Form 3455. No concerns were raised regarding the overall integrity of the data. There was one investigator with disclosable financial arrangements. This investigator was not a principal investigator

Table 59: Summary of Disclosable Financial Arrangements and Interest

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
(b) (6)	INC280A2201	(b) (6)	$360,000	Research Funding

The FDA's Assessment:

FDA agrees with Novartis position. For study A2201, only (b) (6) out of (b) (6) patients enrolled were

recruited at site (b) (6). The financial interests identified above are not expected to affect the study results for ORR and DOR given the (b) (6) enrolled by the investigator identified as having disclosable financial interests. Novartis reported that a total of 1520 out of 1533 (99.2%) principal investigators and sub-investigators responded and provided study-specific financial disclosure forms.

Covered Clinical Study (Name and/or Number):* Study A2201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1533		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

1. Population Pharmacokinetic Analyses

The goal of population PK analysis (popPK) was to develop a population pharmacokinetic (PK) model to assess sources of variability (intrinsic and extrinsic covariates) of capmatinib in patients.

The population PK model for capmatinib included 501 patients with 3846 quantifiable capmatinib concentrations pooled from 4 studies X1101, X2102, A2108 and A2201. Baseline characteristics of patients included in the popPK analysis was provided in Table 60.

The popPK analysis was conducted by the sponsor and evaluated by the reviewer. The PK of capmatinib was characterized by a two-compartment model with delayed zero-order absorption and first-order elimination from the central compartment. The residual error model was described by a proportional and additive error model.

A full covariate modeling approach was implemented to investigate the effects of covariate on capmatinib. After the base model was identified, pre-specified covariates were added to the PK parameters clearance and central volume of distribution, then a final model was established from reduction of the full model by removing covariates per predefined criteria. Criteria considered for inclusion of covariates in the final model are: 1) If the individual PK parameters were well estimated (low shrinkage, low RSE%) 2) From full model, the 95% CI excluded 0 for continuous variable or 1 for categorical variables.

Parameter estimates of full and final model were provided in
Table 61 and

Table 62. The final model included effects of weight and Asian/non-Asian on CL/F as well as an effect of food status and formulation on absorption parameters (ALag, D1, F1). No signs of model misspecification were identified in the goodness-of-fit plots (

Figure 11). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of capmatinib (

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Figure 12). The effects of all evaluated covariates on the capmatinib in the full model were illustrated in the forest plot (

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Figure 13).

No clinically meaning effects on the PK of capmatinib were identified for age (26 to 90 years), sex, race (White and Asian), body weight (35 to 131 kg), mild to moderate renal impairment (baseline creatinine clearance [CRCL] 30 to <90 mL/min), mild hepatic impairment (National Cancer Institute [NCI] hepatic). The 95% CIs of the magnitude of the effects were all contained within 0.8 and 1.25 for clearance at baseline and AUC at steady state.

The observed capmatinib concentration-time profile and post-hoc capmatinib CL were similar between subjects with normal liver function (N=207) and subjects with mild hepatic impairment (N=89) (Figure 14). They were also similar between subjects with normal renal function (N=143) and subjects with mild renal impairment (N=101) and subjects with moderate renal impairment (N=49) (Figure 15).

Table 60: Baseline Characteristics of Patients in the PopPK Analysis Dataset

Demographic variables	All subjects (N=501)
Age (years)	
N	501
Mean (SD)	62.41 (11.08)
Median	63
Q1-Q3	57-70
Min-Max	26-90
Age category (years) - n (%)	
<65	266 (53.1)
≥65	235 (46.9)
Gender - n (%)	
Female	194 (38.7)
Male	307 (61.3)
Asian - n (%)	
Yes	167 (33.3)
No	334 (66.7)
Japanese - n (%)	
Yes	88 (17.6)
No	413 (82.4)
Weight (kg)	
N	501
Mean (SD)	68.66 (15.45)
Median	67.2
Q1-Q3	57-78
Min-Max	35-131
Weight category (kg) - n (%)	
<60	157 (31.3)
60-80	241 (48.1)
>80	103 (20.6)
Albumin (U/L)	
N	501

Mean (SD)	39.58 (4.65)
Median	40
Q1-Q3	37-43
Min-Max	23-50
Alanine aminotransferase (g/L)	
N	501
Mean (SD)	25.29 (17)
Median	21
Q1-Q3	16-29
Min-Max	7-123
Aspartate aminotransferase (g/L)	
N	501
Mean (SD)	25.29 (17)
Median	21
Q1-Q3	16-29
Min-Max	7-123
Bilirubin (umol/L)	
N	501
Mean (SD)	7.56 (4.66)
Median	6
Q1-Q3	4-9.58
Min-Max	1.71-35
Creatinine Clearance (mL/min)	
N	501
Mean (SD)	87.76 (30.12)
Median	82.83
Q1-Q3	65.91-105.28
Min-Max	30.94-238.93
Glomerular filtration rate (mL/min/1.73m^2)	
N	501
Mean (SD)	90.29 (28.95)
Median	85.55
Q1-Q3	70.54-104
Min-Max	28.28-333.43
Hepatic impairment (NCI) - n (%)	
Normal	425 (84.8)
Mild	72 (14.4)
Moderate	4 (0.8)
Renal impairment - n (%)	
Normal	207 (41.3)
Mild	200 (39.9)

Moderate	94 (18.8)

Source: Applicant's PopPK report, Table 5-4, Page 32

Table 61: Parameter Estimates of the Full PopPK Model for Capmatinib

Parameter (unit)	Estimate	SE	RSE (%)	CV (%)	Shrinkage (%)
CL (L/h)	17	0.528	3.11		
V1 (L)	70.3	39.4	56.05		
ALAG1 (h)	0.056	0.008	14.29		
D1 (h)	1.07	0.919	85.89		
Q (L/h)	5.04	2.45	48.61		
V2 (L)	102	16.9	16.57		
Form~ALAG1	8.29	0.050	0.61		
Food~ALAG1	12.6	0.288	2.29		
Form~D1	1.65	2.28	138.18		
Food~D1	3.52	1.23	34.94		
Form~F1	0.638	0.444	69.59		
Food~F1	0.806	0.293	36.35		
Age~CL	-0.126	0.903	716.67		
Weight~CL	0.618	0.582	94.17		
Hepatic Function~CL	0.983	0.431	43.85		
Baseline Albumin~CL	0.249	0.378	151.81		
Baseline Creatinine Clearance~CL	-0.074	0.385	520.27		
Gender~CL	1.09	0.19	17.43		
Japanese~CL	1.08	0.156	14.44		
Weight~V1	0.942	1	106.16		
Baseline Albumin~V1	-0.031	1.2	3870.97		
ω^2_{CL}	0.231	0.076	32.90	50.98	8.93
$\omega^2_{CL\sim V1}$	0.16	0.174	108.75		
ω^2_{V1}	0.177	0.796	449.72	44.00	23.93
ω^2_{ALAG1}	1.21	0.39	32.23	153.41	42.86
$\omega^2_{ALAG1\sim D1}$	0.312	0.155	49.68		
ω^2_{D1}	0.634	0.137	21.61	94.08	40.00
ω^2_{Q}	1.15	0.556	48.35	146.91	32.91
$\omega^2_{Q\sim V2}$	1.4	0.31	22.14		
ω^2_{V2}	2.89	1.85	64.01	412.23	36.22
σ^2_{prop}	0.15	0.026	17.33		
$\sigma^2_{additive}$	35.4	26.2	74.01		

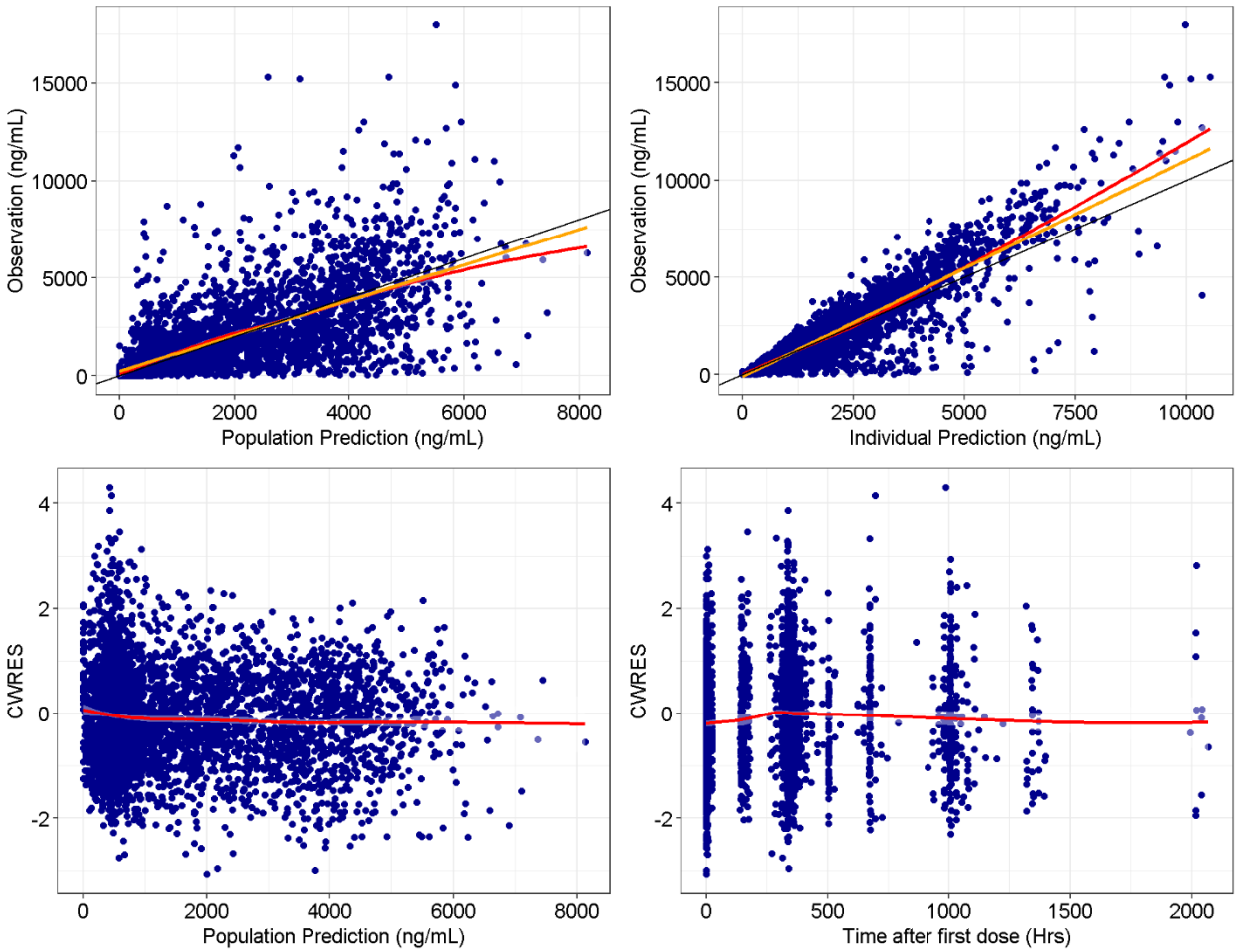
Source: Applicant's PopPK report, Table 5-9, Page 48

Table 62: Parameter Estimates of the Final PopPK Model for Capmatinib

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		

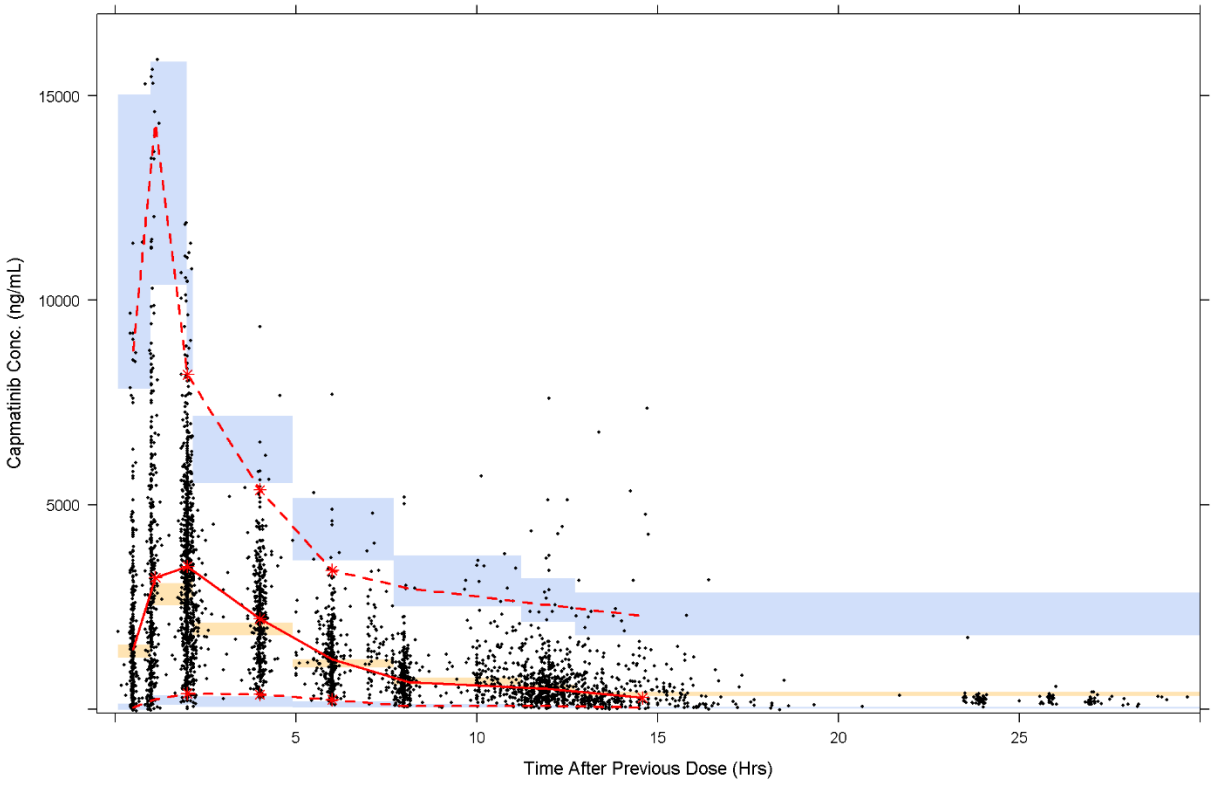
Source: Applicant's PopPK report, Table 5-12, Page 51

Figure 11: Goodness of Fit Plots of the Final Model for Capmatinib



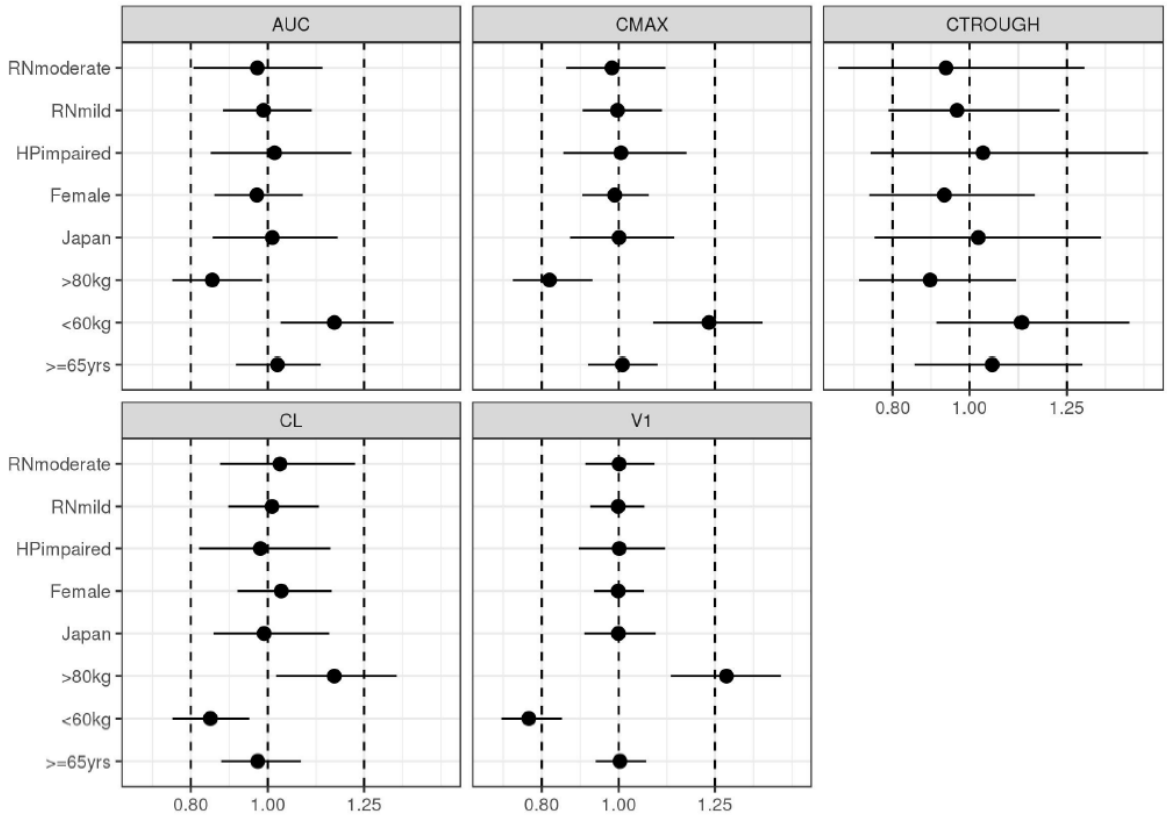
Source: Reviewer's Analysis based on data "pk.comb.csv"

Figure 12: Visual Predictive Checks of Capmatinib Concentration-Time Data.



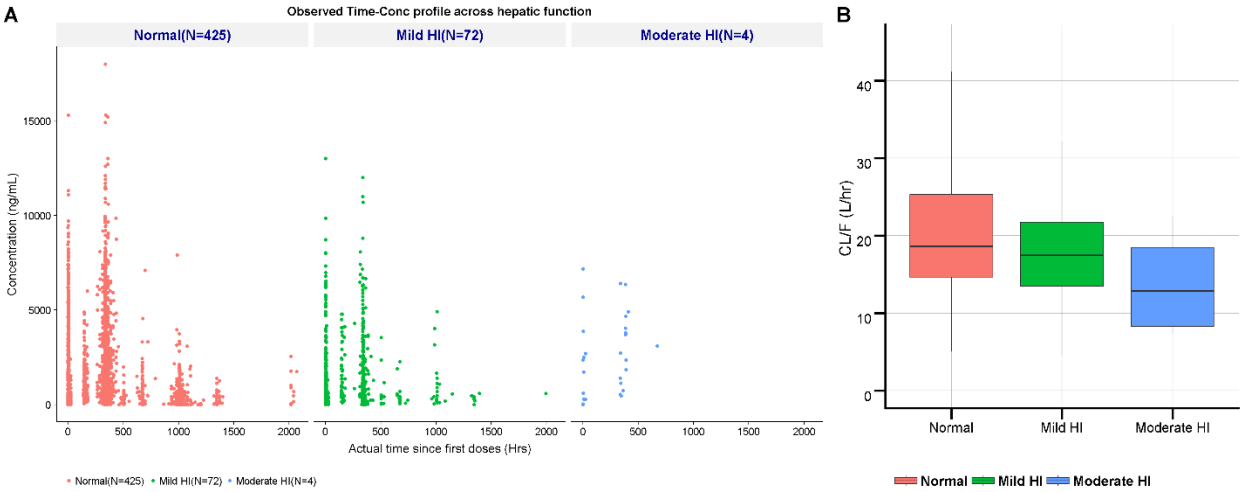
Source: Reviewer's Analysis based on data "pk.comb.csv"

Figure 13: Covariate Effects on Capmatinib Pharmacokinetic Parameters



Source: Applicant's Poppk report, Figure 15 and Figure 16

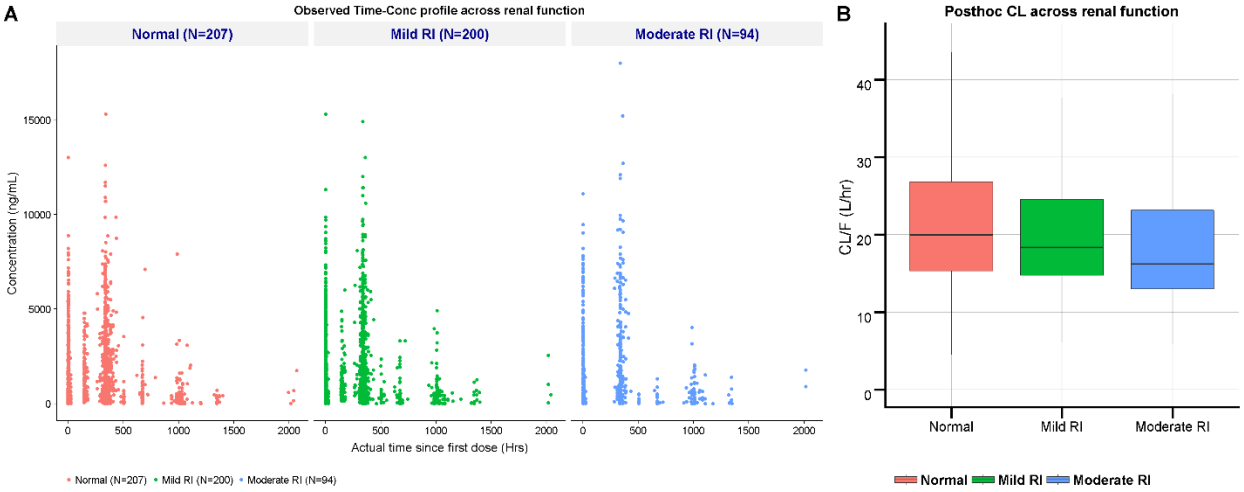
Figure 14: Comparison of Capmatinib PK across Hepatic Function.



Panel A: Observed PK profile across Time
Panel B: Comparison of post-hoc CL across hepatic function

Source: Reviewer's Analysis based on data "pk.comb.csv"

Figure 15: Comparison of Post-hoc CL across Renal Function.



Panel A: Observed PK profile across Time
Panel B: Comparison of post-hoc CL across renal function

Source: Reviewer's Analysis based on data "pk.comb.csv"

2. Exposure-Response Analyses

1) Methods and Data

Exposure-response analyses were conducted by the applicant to explore the relationship between exposure of capmatinib and efficacy and safety in patients who received capmatinib.

Efficacy data was available in 67 patients in cohort 4 and 27 patients in cohort 5b with evaluable capmatinib exposure and efficacy endpoints from study A2201.

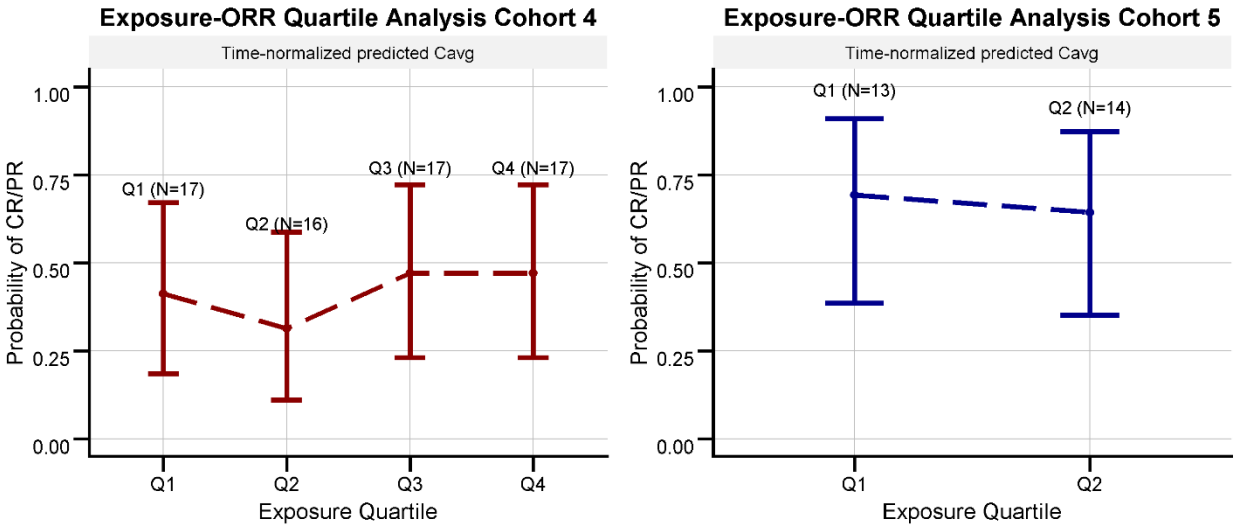
Exposure safety analyses were performed to investigate whether the adverse events could be attributed to the variability in capmatinib. The evaluated adverse events include nausea/vomiting (any grade and grade 3+), amylase and lipase abnormality (any grade and grade 3+). The exposure-safety analyses were conducted in 493 patients from study A2108, A2201, X1101 and X2102.

The primary exposure metrics for exposure-efficacy assessment are individual predicted average, trough concentration for capmatinib from first dose to end of the day of onset of response or censoring. The primary exposure metrics for exposure-safety assessment are individual predicted average, maximum concentration for capmatinib from first dose to end of the day of onset of adverse event or censoring. Graphical quartile analyses were used to investigate the exposure-ORR and exposure-AE relationships.

2) Exposure-ORR Relationships

Overall, there appears to be no trend of exposure-response relationship for ORR in cohort 4 and cohort 5b (Figure 16). However, caution should be taken when interpreting this relationship as it was based on a small sample size with one dosing regimen. The baseline covariates appeared to be different across exposure quartiles in the exposure-ORR analyses (Table 64). But it is probably due to small sample size in each quartile and no consistent trend was observed.

Figure 16: Relationship between Capmatinib Exposure and ORR in Cohort 4 and 5b.



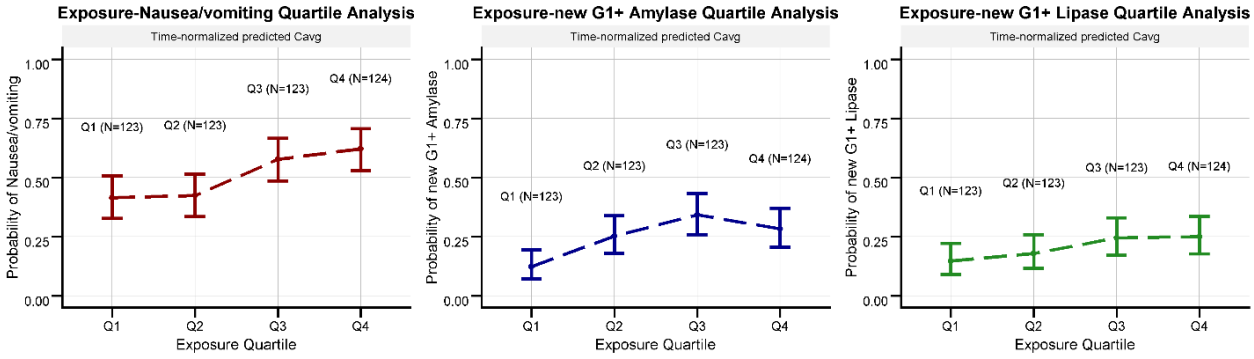
Source: Reviewer's Analysis based on "adpcef.xpt"

3) Exposure-safety Relationships

Graphical quartile analyses suggest higher capmatinib concentration were associated with increased risk of nausea/vomiting events, as well as newly occurred all grades of abnormalities in levels of lipase and amylase (Figure 17). Statistically significant positive associations were observed between capmatinib exposure and occurrence of pancreatic enzyme abnormalities and occurrence of nausea/vomiting events in subjects with solid tumors based on logistic regression model. The baseline covariates across all exposure quartiles in the exposure-safety analyses appeared to be balanced (Table 63).

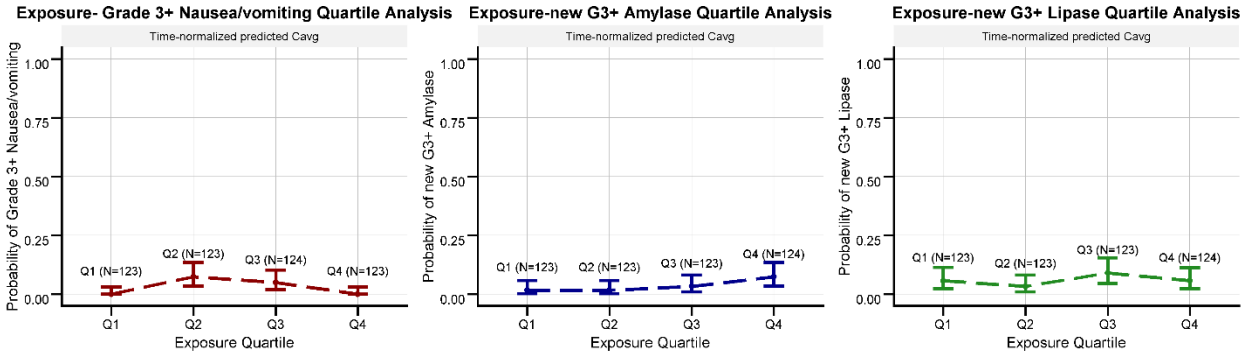
Graphical quartile analyses were also explored to evaluate the relationship between capmatinib concentration and grade 3+ nausea/vomiting events, as well as newly occurred grade 3+ abnormalities in levels of lipase and amylase. A trend of higher grade 3+ abnormalities in levels of amylase in patients with higher capmatinib exposure was observed, but the slope appears to be very shallow (Figure 18). Similar trend was not identified for grade 3+ abnormalities in levels of lipase or grade 3+ nausea/vomiting.

Figure 17：Relationship between Capmatinib Exposure and Adverse Events of Any Grade.



Source: Reviewer's Analysis based on "adpksftd.xpt"

Figure 18：Relationship between Capmatinib Exposure and Grade 3+ Adverse Events.



Source: Reviewer's Analysis based on "adpksftd.xpt"

Table 63：Baseline Covariates across X Exposure Quartiles in the Exposure-Safety Analyses.

Covariate	Value	Q1	Q2	Q3	Q4
Number of Subjects		123	123	123	124
Body Weight		71 (16.9)	69.9 (13.8)	66.9 (15.6)	62 (13.5)
Age		62 (11.2)	62 (11.4)	63 (10.9)	65 (11)
ECOG	>=2	NA	1 (0.8%)	NA	1 (0.8%)
ECOG	0	49 (39.8%)	41 (33.3%)	43 (35%)	39 (31.5%)
ECOG	1	74 (60.2%)	81 (65.9%)	80 (65%)	84 (67.7%)
Race	AMERICAN INDIAN OR ALASKA NATIVE	NA	NA	NA	1 (0.8%)
Race	ASIAN	41 (33.3%)	42 (34.1%)	31 (25.2%)	53 (42.7%)

Race	BLACK OR AFRICAN AMERICAN	2 (1.6%)	NA	NA	NA
Race	OTHER	NA	1 (0.8%)	NA	NA
Race	UNKNOWN	2 (1.6%)	1 (0.8%)	3 (2.4%)	NA
Race	WHITE	78 (63.4%)	79 (64.2%)	89 (72.4%)	70 (56.5%)
Gender	F	37 (30.1%)	40 (32.5%)	55 (44.7%)	57 (46%)
Gender	M	86 (69.9%)	83 (67.5%)	68 (55.3%)	67 (54%)

Source: Reviewer's Analysis based on "adpksftd.xpt"

Table 64：Baseline Covariates across X Exposure Quartiles in the Exposure-Efficacy Analyses.

Cohort 4:

Covariate	Value	Q1	Q2	Q3	Q4
Number of Subjects		17	16	17	17
Body Weight		72.2 (14.6)	68.2 (14.9)	63 (16.5)	55.8 (10.1)
Age		71 (8)	72.5 (10.1)	71 (7.3)	70 (8.7)
ECOG	>=2	NA	NA	NA	1 (5.9%)
ECOG	0	7 (41.2%)	2 (12.5%)	3 (17.6%)	4 (23.5%)
ECOG	1	10 (58.8%)	14 (87.5%)	14 (82.4%)	12 (70.6%)
Race	AMERICAN INDIAN OR ALASKA NATIVE	NA	NA	NA	1 (5.9%)
Race	ASIAN	2 (11.8%)	6 (37.5%)	4 (23.5%)	7 (41.2%)
Race	WHITE	15 (88.2%)	10 (62.5%)	13 (76.5%)	9 (52.9%)
Gender	F	10 (58.8%)	7 (43.8%)	11 (64.7%)	11 (64.7%)
Gender	M	7 (41.2%)	9 (56.2%)	6 (35.3%)	6 (35.3%)

Cohort 5b

Covariate	Value	Q1	Q2
Number of Subjects		13	14
Body Weight		59.9 (14.2)	68.4 (17.8)
Age		71 (6.7)	72.5 (7.7)
ECOG	0	2 (15.4%)	5 (35.7%)
ECOG	1	11 (84.6%)	9 (64.3%)
Race	ASIAN	2 (15.4%)	2 (14.3%)
Race	WHITE	11 (84.6%)	12 (85.7%)

Gender	F	10 (76.9%)	7 (50%)
Gender	M	3 (23.1%)	7 (50%)

Source: Reviewer's Analysis based on "adpcef.xpt"

3. Physiologically-based Pharmacokinetic (PBPK) Modeling

Executive Summary

The aim of this review is to evaluate the adequacy of the Applicant's PBPK report titled "Development of a physiologically-based pharmacokinetic (PBPK) model for capmatinib using Simcyp and predictions of the interaction of capmatinib with common cytochrome P450 victim and perpetrator drugs" to support the intended uses. Specifically, the Applicant applied the PBPK modeling approach to:
(1) assess the effects of a moderate CYP3A4 inhibitor or inducer on the exposure of multiple dose capmatinib in the fasted state,
(2) assess the effects of the effects of capmatinib on the exposures of bupropion (CYP2B6), repaglinide (CYP2C8), rosiglitazone (CYP2C8), warfarin (CYP2C9), and CYP2C19 (omeprazole).

The Division of Pharmacometrics has reviewed the PBPK report [DMPK R1701418], supporting modeling files, responses to Information Request and concluded the following:

- PBPK analysis predicted an interaction between capmatinib and a moderate CYP3A4 inhibitor (such as fluconazole and erythromycin) may increase capmatinib AUCtau by 30%.
- PBPK analysis predicted an interaction between capmatinib and a moderate CYP3A4 inducer (such as efavirenz) may decrease capmatinib AUCtau by 46%. PBPK analyses are adequate to support labeling language for capmatinib interaction with moderate CYP3A4 inducers.
- PBPK analyses suggested capmatinib is a potential weak inhibitor of CYP2C8 and CYP2C9 pathways. The model predicted the DDI effect of capmatinib (400 mg BID) on a substrate of CYP2C8, CYP2C9 or CYP2C19 may be ≤2-fold. PBPK analyses are adequate to support labeling language for capmatinib interaction with substrates of CYP2C8, CYP2C9 and CYP2C19.
- PBPK analysis could not be used to estimate the DDI effect of capmatinib on a substrate of CYP2B6 (such as bupropion) due to the uncertainty of the relative contribution of CYP2B6 to bupropion clearance in the PBPK model.

Background

Capmatinib clearance was driven by CYP3A and aldehyde oxidase (AO) metabolism, with negligible contribution of biliary and urinary excretion [DMPK R1400185, DMPK R1100027, DMPK R1100191, X2106]. The effects of co-administration of the strong inhibitor (itraconazole)

and inducer (rifampicin) for CYP3A4 on the PK of capmatinib were evaluated in the clinical studies in healthy volunteers under fasting conditions [A2102].

Capmatinib was a reversible inhibitor of CYP1A2, 2C8, 2C9, 2C19 and 3A in HLM [DMPK R1000637] and a time-dependent inhibitor (TDI) of CYP3A and 1A2 in vitro human hepatocytes [DMPK R1600690-01]. Capmatinib was also an in vitro inducer of CYP2B6 mRNA and activity, and CYP2C9 and CYP3A mRNA (but not activity) [DMPK R1400243].

Clinically, a Phase 1 study [A2103] was conducted to evaluate the effects of multiple doses of capmatinib (400 mg BID dosing) on the PK of a single-dose midazolam (2.5 mg) or caffeine (100 mg) in cancer patients. Coadministration of midazolam with capmatinib resulted in a 22% (90%CI: 7-38%) and 9% (90%CI: 1-22%) increase in the Cmax and AUCinf of midazolam. Conversely, coadministration of caffeine with capmatinib resulted in 134% (90%CI: 108-163%) increase in the AUCinf of caffeine with no change in the Cmax.

In vitro studies determined capmatinib to be an inhibitor of OCT1, OAT1, OAT3, P-gp, OATP1B1/3 BSEP, MRP2, BCRP and MATEs [DMPK R1000689, DMPK R1400237, DMPK R1400238, DMPK R1400239, DMPK R1400240].

In vitro, capmatinib displayed a pH-dependent solubility profile, however, the effect of gastric pH-altering drugs (such as PPIs) on capmatinib PK were considered modest [A2101].
The main metabolite of capmatinib is CMN288 (M16), which the systemic exposure (AUC) was 42% of that of the parent in the human ADME study [X2106]. CMN288 is a reversible inhibitor of CYP2C8, 2C9, and 3A in HLM and a TDI of CYP3A [DMPK R1400244]. The static DDI assessments, according to net effect model, showed no in vivo inhibition potential of CMN288 on CYP enzymes (AUCR<1.06) [DMPK R1701418].

In vitro data showed that AO was responsible for the metabolic formation of CMN288 and other minor metabolites. The metabolic fraction of these metabolites was estimated to be up to 40% based on human ADME data [X2106]. The Applicant conducted in vitro studies [DMPKR1701530 and R1800008] and literature research on the potential of known CYP3A perpetrators (namely, itraconazole, rifampin, efavirenz, erythromycin and fluconazole) to interact with AO. The obtained in vitro data in combination with clinical exposure were applied in the static mechanistic model. The Applicant concluded that relevant inhibition and/or induction potential towards AO affecting capmatinib clearance is unlikely [DMPK R1701418].

Methods

PBPK model structure and development

The PBPK analyses were performed using the population-based PBPK software Simcyp® (V18 Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). The PBPK model of capmatinib was developed based on in vitro, human ADME study [X2106] and clinical PK data. Briefly, a first-order absorption model and a minimal PBPK model were used to describe capmatinib PK. The fraction absorbed (fa) of the tablet formulation was estimated to be around 0.8 based on mass balance data (50% of the dose excreted unchanged in feces following 600 mg capsule and 1.5-fold higher bioavailability of the tablet formulation compared to capsule) [X2102]. The absorption rate constant (ka= 0.7 h^{-1}) was optimized to fit the clinical PK data following single dose. Applicant assumed the intestinal metabolism of capmatinib is minimum (Fg =1), and the fraction unbound in enterocytes (fugut) value was set as 0.001. Sensitivity of the impact of fugut value (range =0.0001-1) on capmatinib PK and the predicted DDI with CYP3A4 perpetrators (itraconazole and rifampin) and victim (midazolam) were evaluated.

The unbound fraction in plasma (fup=0.04) and concentration-dependent blood to plasma ratio [1.5 (10-1000 ng/mL), 0.9 (10000 ng/mL)] were determined in vitro [DMPK R1400051]. The distribution parameters (Vss=0.32 L/kg, Vsac=0.05 L/kg, Kin=0.1 h^{-1}, and Kout=0.1 h^{-1}) were estimated based on clinical PK data following single dose in healthy volunteers. The renal clearance was set to zero because urinary excretion was minimal in the human ADME study [X2106]. The apparent oral clearance (CL/F) of 26 L/h was used for the retrograde calculation of enzymes intrinsic clearance. This value represented a mean estimate for the CL/F reported following single-dose in healthy volunteers (CL/F= 35.4 L/h [A2102]) and multiple-dose in the target cancer population (Day 1 CL/F =26.9 L/h, CLss/F= 19.8 L/h [A2201] and PPK estimate CLss/F= 18.4 L/h).

The relative contributions of CYP3A4 (fmCYP3A4) and non-CYP metabolism (which includes AO) to capmatinib clearance were initially assigned as 0.53 and 0.47, respectively. These estimates were based on recovery of CYP-mediated and non-CYP metabolites in the excreta data from the human ADME study [X2106]. The fmCYP3A4 value was later adjusted based on the observed DDI effect with itraconazole in healthy volunteers [A2102] (refer to section Q2). The final values of fmCYP3A4 and non-CYP metabolism were estimated as 0.35 and 0.65, respectively. The calculated CLint values for CYP3A4 and additional intrinsic clearance in human liver microsomes (HLM CLint) were 0.435 µl/min/mg and 105 µl/min/mg, respectively.

Capmatinib was not a substrate of active transport processes in human hepatocytes [DMPK R1000684]. Thus, it was assumed that the hepatic uptake of capmatinib was driven by passive permeation (active hepatic scalar= 1). Capmatinib was a substrate for P-gp in vitro [DMPK R1400515]. Given capmatinib seemingly high permeability in vitro (Caco-2 assay = 24.5 x 10^{-6} cm/s, reference metoprolol=14 x 10^{-6} cm/s [INCYTE-DMB-08.121.1]), it is unlikely the efflux transporter will limit its absorption. Reviewer noted that this assumption may be corroborated

by the saturation of absorption seen at capmatinib high dose for the capsule formulation [X1101].

In-vitro data showed that capmatinib was a reversible inhibitor, TDI and a weak inducer of CYP3A. The CYP3A4 Indmax and IndC50 values were 18.16-fold and 35.93 µM, respectively, based on mean mRNA data calibrated against rifampin in vitro induction data [DMPK R1400243]. The CYP3A4 TDI parameters, KI (inhibitor concentration causing half-maximal inactivation) and kinact values were 13.2 µM (fumic=0.745) and 1.8 h^{-1}, respectively, in HLM [DMPK R1000637]. The CYP3A reversible Ki was 4.3 µM (fumic=0.834) [DMPK R1000637]. Simulations using the in vitro CYP3A interaction parameters overpredicted the observed DDI effect of capmatinib on the sensitive CYP3A substrate midazolam (the observed midazolam AUC ratio is 1.09 in the study A2103). The CYP3A4 TDI KI value of capmatinib was adjusted to 100 µM to recover the observed midazolam AUC ratio. Applicant noted that no TDI effect on CYP3A activity was observed in hepatocytes assay [DMPK R1600690-01].

Competitive inhibition models were used to simulate the interaction between capmatinib and the respective index CYP substrates. The in vitro Ki values for CYP1A2, 2C8, 2C9, and 2C19 were 11.3 µM (fumic=0.812), 0.9 µM (fumic=0.812), 3 µM (fumic=0.834), and 6.1 µM (fumic=0.745), respectively. The fraction unbound in microsomes (fumic) was estimated in the in vitro system [DMPK R1000637]. Simulations were also conducted using Ki values at least 10-fold lower than those determined in vitro to account for uncertainty associated with the in vitro estimates.

The CYP2B6 Indmax and IndC50 values were 10.6-fold and 24.7 µM, respectively, based on the mean mRNA data. For CYP2C9, Indmax and IndC50 values were 2.35-fold and 39.4 µM, respectively [DMPK R1400243]. No induction risk is predicted for CYP2C9 based on the R3 algorithm (R=0.8). Thus, CYP2C9 induction parameters were not used as input in capmatinib model.

Simulations were performed using the default healthy volunteer virtual population models (software's library, V18). The Applicant also developed a virtual "Modified Sim-Cancer" population model to characterize the target cancer population. The Applicant's "Modified Sim-Cancer" population model was derived from the default cancer population model (software's library, V18) with an additional 20% reduction in the hepatic and intestinal CYP3A4 abundance. The Applicant rationale is based on the observation of underestimation of exposure to sensitive CYP3A4 substrates in cancer patients. It has been suggested that a reduction in the abundance of CYP3A4 better captures the observed PK of a subset of oncology drugs in cancer patients [1].The Applicant tested the proposed "Modified Sim-Cancer" population model against the PK data of midazolam control group from the study A2103.

[1] 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; 103:271-280.

The default compound models (software's library, V18) for itraconazole, efavirenz, rifampin, erythromycin, fluconazole, midazolam, repaglinide, rosiglitazone, warfarin, omeprazole, and bupropion were used in the PBPK simulations for the respective DDIs. DDI simulations were also conducted using a newly developed PBPK model for itraconazole and its hydroxyl metabolite ("IQ model")[2].

The capmatinib model performance was evaluated by comparing the predicted concentration-time profiles and PK parameters with clinical PK data. The clinical studies included evaluation of 200 mg-600 mg single dose (tablet) in healthy volunteers [A2102, A2106, A2109, X2103, X2107, and A2101] and 400 mg BID (tablet) in the target cancer patients [A2201 and X2102].

PBPK model application

The PBPK model of capmatinib was applied to predict the following:

- Effect of capmatinib on the PK of rosiglitazone and repaglinide (CYP2C8 substrate),
- Effect of capmatinib on the PK of bupropion (CYP2B6 substrate),
- Effect of capmatinib on the PK of omeprazole (CYP2C19/CYP3A4 substrate),
- Effect of capmatinib on the PK of warfarin (CYP2C9 substrate),
- Effect of the moderate CYP3A inhibitors erythromycin and fluconazole on the PK of capmatinib,
- Effect of the moderate CYP3A inducer efavirenz on the PK of capmatinib.

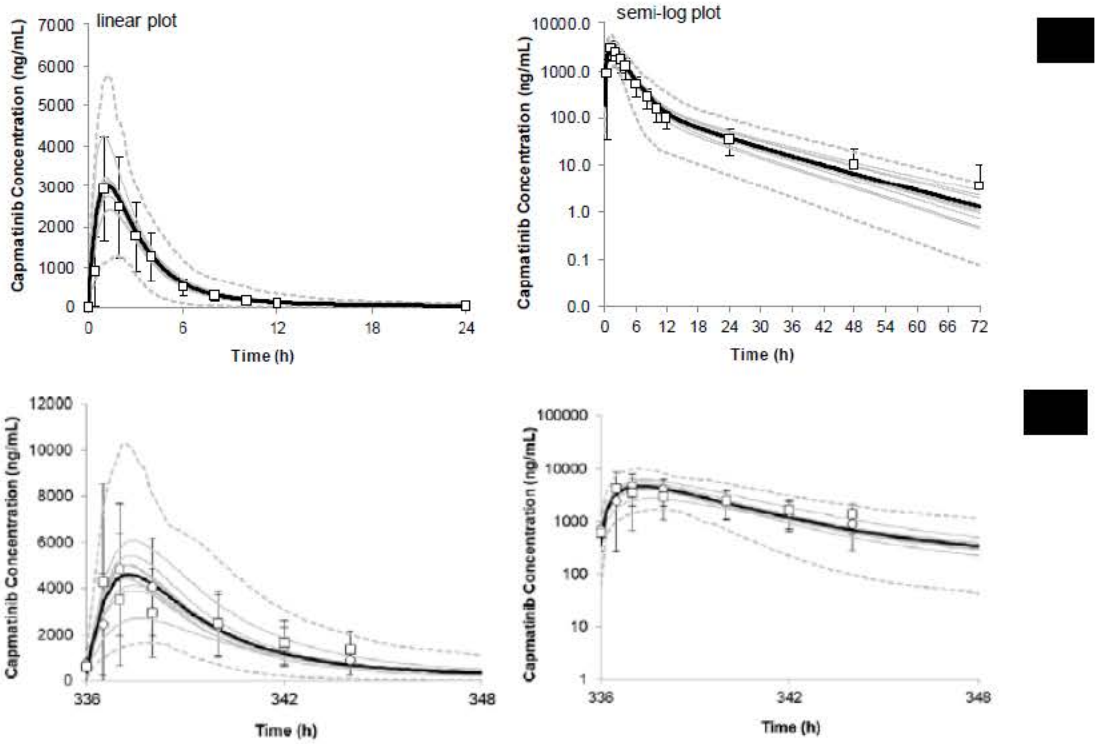
Results

Q1. Can PBPK analyses provide a reasonable description of the PK of capmatinib?

Yes, PBPK simulations reasonably predicted the PK profile of capmatinib following single dose in healthy subjects and multiple dose in the target cancer patients (Figure 19). There was a reasonable agreement between predicted and observed values for AUC and Cmax in healthy volunteers (single 200 mg to 600 mg dose levels) and the cancer patients (400 mg BID) (Table 65).

[2] Chen Y, Cabalu TD, Callegari E, et al. (2019) Recommendations for the design of clinical drug-drug interaction studies with itraconazole using a mechanistic physiologically-based pharmacokinetic model. CPT Pharmacometrics Syst Pharmacol; 8:685-695.

Figure 19: PBPK predicted and observed PK profiles of capmatinib



PBPK predicted mean (bold lines) and observed (symbols: the mean and error bars: standard deviation) plasma concentration-time profiles of capmatinib (A) following a single oral dose of 400 mg in healthy subjects and log-transformed concentration profiles [Study X2103], (B) following 400 mg BID on Day 15 and log-transformed concentration profiles [Studies A2201 and X2102]. The dashed grey lines are the 5% and 95% percentiles and solid grey lines are the means of the individual simulated trials (n=10 x 10) (Source: DMPK R1701418, Figure 7-3 and Response to IR-14, Figure 2-7).

Table 65: Comparison of PBPK predicted and observed Cmax and AUC values of capmatinib

Capmatinib Dosing Regimen	Trial	Observed		Virtual population	Predicted		PE%	
		Cmax (ng/mL)	AUC (ng.hr/mL)		Cmax (ng/mL)	AUC (ng.hr/mL)	Cmax	AUC
200 mg SD	A2102	1380	5500	Healthy	1516	6730	10	22
	A2106	1470	5630				3	20
300 mg SD	A2109	2070	7190	Healthy	2334	10100	13	40
400 mg SD	A2102	3330	11600	Healthy	3193	13473	-4	16
600 mg SD	X2107	4640	17500	Healthy	5022	20230	8	16
	X2103	5200	16500				-3	23
	A2101	4860	17600				3	15
400 mg BID	A2201	5450	23000	Healthy	4694	19710	-14	-14
	X2102	4910	22000				-4.4	-10
	A2201	5450	23000	Sim-Cancer	4612	19421	-15	-16
	X2102	4910	22000				-6	-12
	A2201	5450	23000	Modified Sim-Cancer	4832	20801	-11	-9.5
	X2102	4910	22000				-1.6	-5.5

A PK data are presented as means. AUCinf for SD and $AUC_{0\text{-}12h,ss}$ (AUCtau) for BID. PE% is the calculated prediction error (%) = [(predicted value – observed value)/observed value] x 100. (Source: DMPK R1701418, Table 6-2 and Response to IR-14, Table 2-8).

A comparison of the predicted PK parameters for capmatinib was conducted using the default healthy and cancer virtual population models (software's library, V18) and the Applicant's "Modified Sim-Cancer" population model. The predicted PK of capmatinib in patients simulated with the different population models were comparable. The PE ranged from -16% to -2% across the population models (Table 65).

Q2. Can PBPK analyses predict the effect of a CYP3A4 modulator on the PK of capmatinib?
The contribution of the CYP3A4 pathway to capmatinib clearance (e.g., assumption of fmCYP3A4) was optimized using clinical DDI data with the strong CYP3A inhibitor itraconazole. The fmCYP3A4 assumption was then tested against the clinical DDI with the strong CYP3A inducer rifampin.

During model development, it was initially assumed an fmCYP3A4 value of 0.53, based on in vitro and ADME human data. The predicted DDI effect of itraconazole was overestimated: the predicted geometric mean ratios for AUCinf were 2.13 and 1.84, using the default itraconazole model (software's library V18) or the IQ model, respectively, compared with the reported ratio of 1.42 (90%CI: 1.33-1.52) (Table 66). Because the predicted AUCinf ratios were at least 30% above the observed data (an acceptance criterion proposed by the Applicant), the Applicant conducted sensitivity analysis for the value of fmCYP3A4 to recover the observed DDI effect of itraconazole on capmatinib PK.

An fmCYP3A4 value of 0.35 allowed the recovery of the observed AUCinf ratios in the presence of itraconazole: the predicted ratios were 1.57 and 1.45, using the default itraconazole model

or the IQ model, respectively, versus the observed ratio of 1.42 (Table 66). The fmCYP3A4 value of 0.35 was then assigned in the PBPK model of capmatinib.

Table 66: Comparison of observed and predicted Cmax and AUC values of capmatinib in the absence and presence of itraconazole

Treatment	Cmax (ng/mL)		AUCinf (ng.h/mL)		Cmax Ratio (90%CI)		AUCinf Ratio (90%CI)	
	Pred	Obs	Pred	Obs	Pred	Obs	Pred	Obs
Capmatinib fmCYP3A4= 0.35								
Control	1401	1260	6363	5180	1.26 (1.24-1.28)	1.03 (0.87-1.22)	1.57 (1.52-1.62)	1.42 (1.33-1.52)
with ITZ *default model*	1764	1300	9986	7360				
with ITZ *IQ model*	1822		9300		1.23 (1.22-1.25)		1.45 (1.42-1.49)	
Capmatinib fmCYP3A4= 0.53								
Control	1567	1260	7127	5180	1.43 (1.39-1.46)	1.03 (0.87-1.22)	2.12 (2.03-2.21)	1.42 (1.33-1.52)
with ITZ *default model*	2118	1300	15030	7360				
with ITZ *IQ model*	2169		13134		1.38 (1.36-1.41)		1.84 (1.79- 1.90)	

PK data are presented as geometric means. Cmax ratio and AUC ratio were expressed as with inhibitor/without inhibitor. Simulations were conducted using the healthy volunteer population model. The default itraconazole model from software's library V18 or the proposed itraconazole IQ model were used, as indicated. Simulation design: a single 200 mg capmatinib dose (on day 6) with and without 200 mg itraconazole solution (day 1-10), age range of 21-55 years, proportion of female=0, and 10 trials of 10 subjects. Observed values from study CINC280A2102. (Source: DMPK R1701418, Table 6-4, Response to IR-14, Table 2-6, Reviewer's analysis).

The fmCYP3A4 value of 0.35 was tested against the clinical DDI with rifampin. The predicted Cmax and AUCinf ratios of capmatinib in the presence of rifampin were 0.60 and 0.45, respectively, compared with the reported Cmax and AUCinf ratios of 0.44 and 0.34, respectively (Table 67). The predicted values yielded a PE around -35% for the DDI effect of rifampin on capmatinib Cmax and AUC. Conversely, the initial assumption of an fmCYP3A value of 0.53 yielded a PE around 7% to 18%, for AUC and Cmax ratios, respectively.

Table 67: Comparison of observed and predicted Cmax and AUC values of capmatinib in the absence and presence of rifampin

Treatment	Cmax (ng/mL)		AUCinf (ng.h/mL)		Cmax ratio (90%CI)		AUCinf ratio (90%CI)	
	Pred	Obs	Pred	Obs	Pred	Obs	Pred	Obs
Capmatinib fmCYP3A4= 0.35								
Control	2961	3070	12739	11500	0.60 (0.50-0.63)	0.44 (0.39-0.50)	0.45 (0.43-0.47)	0.34 (0.30- 0.37)
With rifampin	1789	1350	5723	3850				
Capmatinib fmCYP3A4= 0.53								
Control	3153	3070	14206	11500	0.52 (0.50, 0.55)	0.44 (0.39-0.50)	0.36 (0.34, 0.38)	0.34 (0.30- 0.37)
With rifampin	1645	1350	5090	3850				

PK data are presented as geometric means. Cmax ratio and AUC ratio were expressed as with inhibitor/without inhibitor. Simulations were conducted using the healthy volunteer population model. Simulation design: a single 400 mg capmatinib dose (on day 6) with and without 600

mg rifampin (day 1-9), age range of 21-55 years, proportion of female=0., 10 trials of 10 subjects. Observed values from study CINC280A2102. (Source: DMPK R1701418, Table 6-5 and Response to IR-14, Table 2-6).

The Applicant acknowledged that although the DDI effect of itraconazole was better predicted with a lower fmCYP3A4 for capmatinib (Table 66), this fmCYP3A4 value (= 0.35) underpredicted the DDI effect of rifampin (Table 67). The Applicant suggested that rifampin may induce other enzymes involved in capmatinib clearance and/or an incomplete inhibition of CYP3A4 metabolism by itraconazole. However, it is unlikely that rifampin is inducing AO pathway because rifampin did not show potential for in vitro [DMPK R1701530].

Reviewer's comments:

Given the remaining uncertainty on the fmCYP3A4 of capmatinib and the "top-down" approach of capmatinib PBPK model, the reviewer requested the Applicant to evaluate key input parameters that may affect the evaluation of capmatinib as victim of CYP3A4-mediated interaction. The Applicant conducted sensitivity analysis for the values of fugut (0.001, 0.04 and 1), fmCYP3A4 (0.35 and 0.53), CYP3A4 interaction parameters, and virtual population models (healthy, Sim-Cancer and "Modified Sim-Cancer"). A single-point SA was conducted, which did not take into consideration the correlation among such parameters.

Although the reviewer acknowledges limitations on the current capmatinib model and SA, the following inferences about the fmCYP3A4 value can be derived from the information available:

- The Applicant refines the fmCYP3A4 assumption from 0.53 to 0.35 based on clinical data with itraconazole. Two different PBPK models for this perpetrator were used: the default from software's library and the new IQ model. Based on results on Table 65 (under fmCYP3A4= 0.53), the default model provided higher inhibition effect by itraconazole compared to the IQ model. The Applicant refined the fmCYP3A4 value based on the IQ model. This approach led to an fmCYP3A value of 0.35. On the other hand, if the default model was used to refine fmCYP3A4 value, an even lower value for fmCYP3A4 would be derived. On other words, by using the IQ model, a higher contribution of CYP3A4 to capmatinib clearance was assumed, thus, a more conservative scenario for DDI risk evaluation.
- Although the refined fmCYP3A value of 0.35 resulted in an underprediction of capmatinib clinical DDI with rifampin, the reviewer recognizes limitations of using clinical induction data to inform fmCYP values. First, rifampin is a strong inducer of several CYPs and other metabolic pathways. Second, a general trend of underprediction of clinical CYP3A induction by PBPK analysis has been noted.[3] Third, for capmatinib model specifically, further exploring the fmCYP3A4 value of 0.35 but with a different set of input parameters for capmatinib, such as a higher fugut value (=1), resulted in a better prediction (PE%= 2) of rifampin clinical

[3] Grimstein M, Yang y, Zhang X et al. (2018). Physiologically-based Pharmacokinetic (PBPK) Modeling in Regulatory Science: An Update from the US Food and Drug Administration's Office of Clinical Pharmacology, J Pharm Sci. 108: 21-25.

DDI. Reviewer notes the predicted DDI effect with itraconazole using fmCYP3A value of 0.35 and fugut =1 is within 15% of that simulated with the current capmatinib model.

- The initial assumption of an fmCYP3A4 of 0.53, derived from the human ADME study, is a conservative estimate. It assumed that any identified CYP metabolites in the excreta data was mediated by CYP3A4. For metabolites with multiple oxidations in which all the enzyme(s) involved could not be identified, were assumed in-part to be mediated by CYP3A4 [DMPK R1701418].
- Taking into consideration the totality of evidence, namely, the conservative estimation for fmCYP3A4 from human ADME data, the range of fmCYP3A4 values, and most importantly, the weak clinical DDI effect observed with the strong CYP3A4 inhibitor itraconazole, and moderate clinical DDI effect with the strong CYP3A inducer rifampin, an assumption of fmCYP3A value of 0.35 seems reasonable to predict the DDI risk of capmatinib with moderate CYP3A perpetrators.

Q3. Can PBPK analyses be used to estimate the effect of a moderate CYP3A4 perpetrator on capmatinib PK?

Yes. The DDI effect of a moderate CYP3A4 inhibitor or inducer on capmatinib exposure can be estimated by PBPK analyses.

The predicted increase on capmatinib exposure at steady-state (AUC_{tau}) was 30% with coadministration of the moderate CYP3A4 inhibitors fluconazole and erythromycin. The predicted decrease on capmatinib exposure at steady-state was 46% with coadministration of the moderate CYP3A4 inducer efavirenz (Table 68).

Table 68: Predicted Cmax and AUC changes of capmatinib in the presence of moderate CYP3A4 perpetrators

Perpetrator		Capmatinib 400 mg SD		Capmatinib 400 mg BID	
Class	**Dosing Regimen**	**Cmax Ratio (90% CI)**	**AUCinf Ratio (90% CI)**	**Cmax Ratio (90% CI)**	**AUCtau Ratio (90% CI)**
CYP3A4 moderate inducer	Efavirenz 600 mg QD	0.68 (0.65, 0.70)	0.54 (0.52, 0.567)	0.65 (0.62, 0.67)	0.54 (0.52, 0.57)
CYP3A4 moderate inhibitor	Erythromycin 500 mg TID	1.19 (1.18, 1.21)	1.36 (1.33, 1.39)	1.20 (1.18, 1.21)	1.30 (1.28, 1.33)
CYP3A4 moderate inhibitor	Fluconazole 200 mg QD	1.20 (1.18, 1.21)	1.35 (1.33, 1.37)	1.19 (1.18, 1.21)	1.30 (1.28, 1.32)

Data are presented as population geometric mean values for exposure ratios (AUC and Cmax) and 90% confidence intervals, expressed as the fold change in the presence versus absence of a perpetrator. Simulations were conducted using the healthy volunteer population model ("NEurCaucasian"). Simulation design: capmatinib 400 mg SD: single dose on Day 6 (for erythromycin) or Day 15 (for fluconazole and efavirenz). Capmatinib 400 mg BID: multiple BID doses [Days 1- 10 (for erythromycin) or 1-20 (for fluconazole and efavirenz)], age range of 37-75 years, proportion of female=0.5, 10 trials of 10 subjects. (Source: Response to IR-14, Table 2-10).

Besides using the default healthy volunteer population model (Table 68), DDI simulations were also conducted using the default cancer population model (software's library, V18) and the

Applicant's "Modified Sim-Cancer" population model. There was no major difference (<10%) in the predicted DDI effect of moderate CYP3A perpetrators on capmatinib PK among the three different population models (Table 68, Table 69).

Table 69: Sensitivity analysis for the effect of a CYP3A perpetrator on steady-state capmatinib using virtual cancer population models

Virtual Population Model		*Sim-Cancer*		*Modified Sim-Cancer*	
Perpetrator Class	**Dosing Regimen**	**Cmax Ratio**	**AUCtau Ratio**	**Cmax Ratio**	**AUCtau Ratio**
CYP3A4 moderate inducer	Efavirenz 600 mg QD	0.63	0.52	0.66	0.56
CYP3A4 moderate inhibitor	Erythromycin 500 mg TID	1.17	1.26	1.14	1.22
CYP3A4 moderate inhibitor	Fluconazole 200 mg QD	1.20	1.30	1.16	1.25

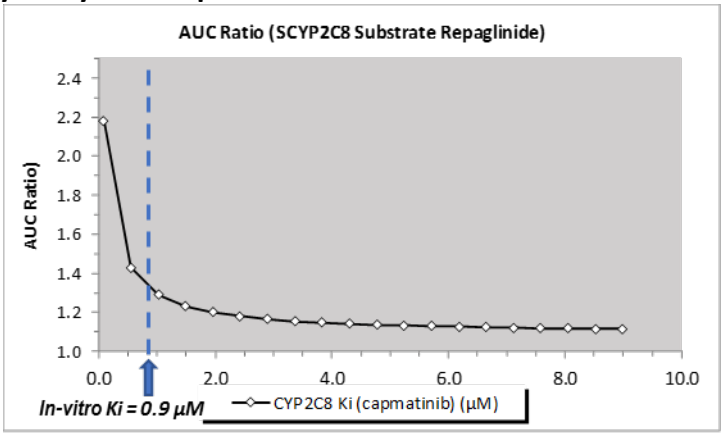
Data are presented as population geometric mean values for exposure ratios (AUC and Cmax) expressed as the fold change in the presence versus absence of a perpetrator. Simulations were conducted using the default Sim-Cancer and the "Modified Sim-Cancer" population models, as shown. Simulation design: Capmatinib 400 mg BID [Days 1- 10 (for erythromycin) or 1-20 (for fluconazole and efavirenz)], age range of 37-75 years, proportion of female=0.5, 10 trials of 10 subjects. (Source: DMPK R1701418, Table 6-9, Response to IR-14, Table 2-10).

Q4. Can PBPK analysis be used to estimate the effects of capmatinib on a CYP2C8 substrate?
Yes. PBPK DDI simulations were conducted between repeated doses of capmatinib (400 mg BID for 9 days) and single dose of repaglinide (0.25 mg on Day 6) or rosiglitazone (4 mg on Day 6), using the healthy volunteer population model.

Repaglinide is a substrate of CYP2C8 and CYP3A4 metabolism and a substrate for OATP1B1-mediated uptake. The current DDI analysis will focus on repaglinide as CYP2C8 and CYP3A4 substrate. The software's repaglinide model has been verified for the contributions of CYP2C8 and CYP3A4 to clearance using the clinical DDI data with clarithromycin (CYP3A inhibitor), itraconazole (a CYP3A inhibitor), trimethoprim (a CYP2C8 inhibitor) and gemfibrozil (dual CYP3A4 and CYP2C8 inhibitor). The contribution of CYP2C8 and CYP3A4 to repaglinide clearance is 60% and 40%, respectively.

The interaction effect of capmatinib on repaglinide in terms of predicted geometric mean ratios for Cmax and AUC were 1.18 and 1.32, respectively. Sensitivity analysis of CYP2C8 Ki value resulted in a 2-fold increase on repaglinide AUC, when a Ki value 10-fold lower than that reported in vitro ($1/10^{th}$ of 0.9 µM) was tested (Figure 20). The predicted geometric mean ratios for repaglinide Cmax and AUC were 1.57 and 2.10, respectively. Thus, capmatinib is a weak inhibitor of CYP2C8. Capmatinib PBPK model included the interaction parameters of CYP3A4 (based on midazolam clinical DDI data) and OATP1B1 (based on in-vitro data) pathways.

Figure 20: Sensitivity analysis of capmatinib Ki value towards CYP2C8



Data are presented as changes in the AUC of repaglinide in the presence of capmatinib as a function of the CYP2C8 inhibition constant (Ki) value. Simulations were conducted using the healthy volunteer population model ("NEurCaucasian"). Simulation design: 400 mg capmatinib BID dose (Day 1- 10) with repaglinide 0.25 mg on Day 6, for 10 days, age range of 37-75 years, proportion of female=0.5, 10 trials of 10 subjects. Source: Reviewer's Analysis using Applicant's workspaces files.

For rosiglitazone, the interaction effect in terms of predicted geometric mean ratios for Cmax and AUC were 1.04 and 1.17, respectively. Sensitivity analysis of CYP2C8 Ki value resulted in less than 2-fold increase of rosiglitazone AUC, even when a Ki value 10-fold lower than that reported in vitro ($1/10^{th}$ of 0.9 µM) was tested. The contribution of CYP2C8 to rosiglitazone clearance is around 50%.

Overall, PBPK simulations suggested low potential for a clinically significant interaction (assumed as AUC ratio >2) between capmatinib and a moderate sensitive CYP2C8 substrate such as rosiglitazone. However, the simulated DDI results of repaglinide showed that capmatinib is a weak inhibitor of CYP2C8.

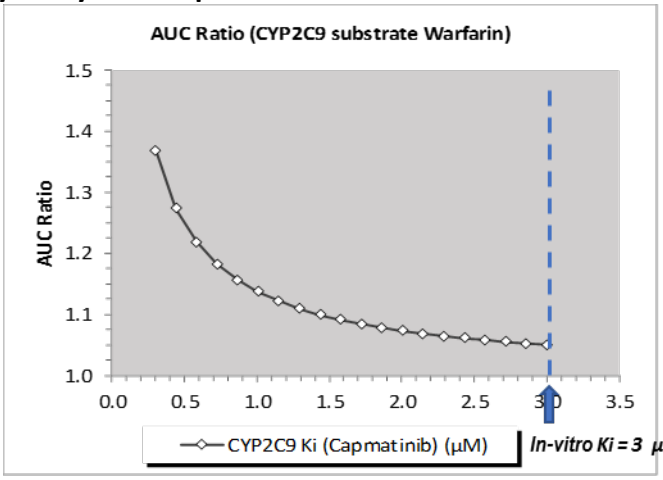
The reviewer acknowledges that the CYP2C8 mediated-DDI risk analysis is limited to the evaluation of inhibition effect of capmatinib. The potential for induction on CYP2C8 has not been evaluated in vitro, although capmatinib has showed to be inducer of CYP3A, 2B6 and CYP2C9 in vitro.

Q5. Can PBPK analysis be used to estimate the effects of capmatinib on a CYP2C9 and CYP2C19 substrate?

Yes. PBPK DDI simulations were conducted between repeated doses of capmatinib (400 mg BID for 9-20 days) and single doses of warfarin (moderate CYP2C9 substrate, 10 mg on Day 6) or omeprazole (sensitive CYP2C19 substrate, 20 mg on Day 6), using the healthy volunteer population model.

For warfarin, the interaction effect in terms of predicted geometric mean ratios for Cmax and AUC were 1.01 and 1.06, respectively. Sensitivity analysis of CYP2C9 Ki value showed a 25% increase in warfarin AUC with a Ki value 6-fold lower than that reported in vitro (1/6th of 3 µM) (Figure 21). The predicted geometric mean ratios for Cmax and AUC were 1.03 and 1.26, respectively. Therefore, PBPK simulations suggested capmatinib is a potential weak inhibitor of CYP2C9.

Figure 21: Sensitivity analysis of capmatinib Ki value towards CYP2C9



Data are presented as changes in the AUC of warfarin in the presence of capmatinib as a function of the CYP2C9 inhibition constant (Ki) value. Simulations were conducted using the healthy volunteer population model ("NEurCaucasian"). Simulation design: 400 mg capmatinib BID dose (Day 1- 20) with warfarin 10 mg on Day 6, for 20 days, age range of 37-75 years, proportion of female=0.5, 10 trials of 10 subjects. Source: Reviewer's Analysis using Applicant's workspaces files.

For omeprazole, the interaction effect in terms of predicted geometric mean ratios for Cmax and AUC were 1.09 and 1.11, respectively. Sensitivity analysis of CYP2C19 Ki value resulted in less than 2-fold increase of omeprazole AUC, even when a 10-fold lower value than that reported in vitro was tested (1/10th of 6.1 µM). Therefore, PBPK simulations suggested low potential for a clinically significant interaction (assumed as AUC ratio >2) between capmatinib and a CYP2C19 substrate such as omeprazole.

Q6. Can PBPK analysis be used to estimate the effects of capmatinib on a CYP2B6 substrate?
No. Limitations were found in the default bupropion library model that precluded its use as a CYP2B6 substrate for estimation of the effect of capmatinib using in vitro data. Bupropion is metabolized by several clearance pathways (CYP2B6, CYP2C19, CYP3A and dehydrogenases) and has a stereoselective metabolism[4]. The software developer has noted there is a divergence between emerging in vitro metabolic data and bupropion clinical DDI data. These factors led to

[4] Sager JE, Price LS, Isoherranen N. (2016) Stereoselective metabolism of bupropion to OH-bupropion, threohydrobupropion, erythrohydrobupropion, and 4'-OH-bupropion in vitro. Drug Metab Dispos.;44:1709-1719.

difficulties in the characterization of contribution of CYP2B6 to bupropion clearance. Given the uncertainty in the fmCYP2B6 value in the bupropion PBPK model, any PBPK simulation predictions are inconclusive.

Conclusion
PBPK modeling was considered adequate to predict the effect of capmatinib on the PK of CYP2C8, CYP2C9 and CYP2C19 substrates. PBPK analyses suggested capmatinib is a potential weak inhibitor of CYP2C8 and CYP2C9. However, clinical interaction between capmatinib (400 mg BID) and a substrate of CYP2C8, CYP2C9 or CYP2C19 is predicted to be ≤2-fold.

The current capmatinib model allowed a reasonable estimate of the CYP3A-mediated DDI risk of capmatinib as a victim drug. A moderate CYP3A4 inhibitor (such as fluconazole and erythromycin) may increase capmatinib AUCtau by 30%, while a moderate CYP3A4 inducer (such as efavirenz) may decrease capmatinib AUCtau by 46%.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
None.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Claire E. Myers, Ph.D.	OOD/DHOT	Sections: 4.2, 5, 19.1, 19.3	Select one: X Authored ___ Approved
	Signature: Claire E. Myers -S Digitally signed by Claire E. Myers -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011079533, cn=Claire E. Myers -S Date: 2020.04.30 10:30:18 -04'00'			
Nonclinical Supervisor	Whitney S. Helms, Ph.D.	OOD/DHOT	Sections: 4.2, 5, 19.1, 19.3	Select one: X Authored X Approved
	Signature: Whitney S. Helms -S Digitally signed by Whitney S. Helms -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000585776, cn=Whitney S. Helms -S Date: 2020.04.30 07:43:01 -04'00'			
Nonclinical Team Division Director	John K. Leighton, Ph.D.	OOD/DHOT	Sections: 4.2, 5, 19.1, 19.3	Select one: ___ Authored X Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2020.04.30 08:37:31 -04'00'			
Clinical Pharmacology Reviewer	Runyan Jin	OCP/DCPI	Section: 6	Select one: X Authored ___ Approved
	Signature: Runyan Jin -S Digitally signed by Runyan Jin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Runyan Jin -S, 0.9.2342.19200300.100.1.1=2000625773 Date: 2020.04.30 14:53:45 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	OCP/DCPII	Section: 6	Select one: X Authored X Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2020.04.30 16:28:55 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman	OCP/DCPII	Section: 6	Select one: ___ Authored X Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2020.05.05 08:21:31 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Youwei Bi	OCP/DPM	Sections: 19.4 (1 popPK analyses and 2 Exposure-Response Analyses)	Select one: X Authored ___ Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Youwei Bi -S, 0.9.2342.19200300.100.1.1=2001767281 Date: 2020.04.30 15:37:59 -04'00'			
Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections: 19.4 (1 popPK analyses and 2 Exposure-Response Analyses)	Select one: X Authored X Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.04.30 14:24:29 -04'00'			
PBPK Reviewer	Manuela Grimstein	OCP/DPM	Section: 19.4 (3 PBPK modeling)	Select one: X Authored ___ Approved
	Signature: Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000561102, cn=Manuela D. Grimstein -S Date: 2020.04.30 15:39:28 -04'00'			
PBPK Team Leader	Yuching Yang	OCP/DPM	Section: 19.4 (3 PBPK modeling)	Select one: X Authored X Approved
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Genomics Reviewer	Jeffrey Kraft	OCP/DTPM	Section: 6.3.2.3	Select one: X Authored _____ Approved
	Signature: Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000828011, cn=Jeffrey B. Kraft Jr -S Date: 2020.05.04 10:04:42 -04'00'			
Genomics Team leader	Rosane Charlab Orbach	OCP/DTPM	Section: 6.3.2.3	Select one: X Authored X Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Luckson Mathieu	OOD/DO2	Sections:1, 2, 3, 4.1, 4.4, 7, 8, 9, 10, 11, 12, 13, 19.2	Select one: X Authored X Approved
	Signature: Luckson Mathieu -S Digitally signed by Luckson Mathieu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001482309, cn=Luckson Mathieu -S Date: 2020.04.30 14:35:03 -04'00'			
Statistical Reviewer	Anup Amatya	OB/DBV	Sections: 8.1, 8.3	Select one: X Authored X Approved
	Signature: Anup K. Amatya -S Digitally signed by Anup K. Amatya -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anup K. Amatya -S, 0.9.2342.19200300.100.1.1=2002706863 Date: 2020.04.30 16:47:45 -04'00'			
Statistical Team Leader	Mallorie Fiero	OB/DBV	Sections: 8.1, 8.3	Select one: X Authored X Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero -S Date: 2020.04.30 10:00:49 -04'00'			
Division Director (OB)	Shenghui Tang	OB/DBV	Sections: 1.0, 8.1, 8.3, 8.4	Select one: X Authored X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9 2342.19200300.100.1.1=1300224175 Date: 2020.05.05 18:38:49 -04'00'			
Associate Director of Labeling	Stacy S. Shord	OND/OOD	Section: 11	Select one: x Authored x Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2020.05.04 08:33:15 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Erin Larkins	DO2/OOD	Sections: All	Select one: X Authored X Approved
	Signature: Erin A. Larkins -S5 Digitally signed by Erin A. Larkins -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011520339, cn=Erin A. Larkins -S5 Date: 2020.05.05 11:20:37 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Division Director (Clinical)	Harpreet Singh	DO2/OOD	Sections: All	Select one: X Authored X Approved
	Signature: Bonnie H. Moore -S Digitally signed by Bonnie H. Moore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001042285, cn=Bonnie H. Moore -S Date: 2020.05.03 21:55:18 -04'00'			

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KELIE M REECE
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B HARPREET SINGH
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MARC R THEORET
05/06/2020 12:35:42 PM
My signature indicates that I have considered the assessments and recommendations included in this Review in determining the regulatory action