CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215310Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA MULTI-DISCIPLINARY REVIEW AND EVALUATION

FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration (TGA), Brazilian Health Regulatory Agency (ANVISA), and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA). While the application review is completed by the FDA, the application is still under review at the other regulatory agencies.

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

Application Type	NDA
Application Number(s)	215310
Priority or Standard	Priority
Submit Date(s)	12/23/2020; 02/26/2021
Received Date(s)	12/23/2020; 02/26/2021
PDUFA Goal Date	10/26/2021
Division/Office	Division of Oncology 2/ Office of Oncologic Drugs
Review Completion Date	September 15, 2021
Established Name	mobocertinib
(Proposed) Trade Name	Exkivity
Pharmacologic Class	Kinase inhibitor
Code name	TAK-788; AP32788 succinate
Applicant	Takeda Pharmaceuticals U.S.A., Inc.
Formulation(s)	capsule
Dosing Regimen	40 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with metastatic non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations (b) (4)

	(b) (4) platinum-based chemotherapy.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs/Patient Labeling Team
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

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GLOSSARY

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AECI	adverse event of clinical interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BIRC	blinded independent review committee
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit-Risk Framework
BTD	break through designation
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	creatine phosphokinase
CR	confirmed overall response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
DCR	disease control rate
DDI	drug-drug interaction
DiC	drug-in-capsule
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee

DOR	duration of response
DRISK	Division of Risk Management
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EGFR	epidermal growth factor receptor
EHR	electronic health record
EMR	electronic medical record
EORTC	European Organisation for Research and Treatment of Cancer
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GI	gastrointestinal
GLP	good laboratory practice
GRMP	good review management practice
FISH	Fluorescence in situ hybridization
HR	Hazard Ratio
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IND	Investigational New Drug
IO	immuno-oncology
IRB	Institutional Review Board
IRC	Independent review committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NDI	National Death Index
NE	Not evaluable

NGS	next generation sequencing
NME	new molecular entity
NNT	Number needed to treat
NR	not reported
NSCLC	non-small cell lung cancer
OCE	Oncology Center of Excellence
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCS	Office of Computational Science
OCT	organic cation transporter
OPQ	Office of Pharmaceutical Quality
ORR	Objective response rate
OS	Overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiologically-based pharmacokinetic
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	Progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per-protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
QD	Once daily
QoL	Quality of life
QTcF	Fridericia heart rate-corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors
RETIC	reticulocyte counts
REMS	risk evaluation and mitigation strategy
RWD	real-world data
SAE	serious adverse event
SAP	statistical analysis plan
SD	Stable disease

SEER	Surveillance, Epidemiology, and End Results
SGE	special government employee
SOC	standard of care
SSDI	Social Security Death Index
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse events
ULN	upper limit of normal
UREAN	urea nitrogen
U.S.	United States
WBC	white blood cell
WT	wild type

1.0 EXECUTIVE SUMMARY

1.1 Product Introduction

Mobocertinib is an irreversible tyrosine kinase inhibitor that forms a covalent bond with cysteine 797 in EGFR, leading to the inhibition of EGFR signaling. At the time of application submission, mobocertinib was not approved for any indication.

The recommended dosage regimen for the proposed indication is 160 mg orally once daily, with or without food.

1.2 Conclusions on the Substantial Evidence of Effectiveness

Takeda has provided substantial evidence of effectiveness supporting the accelerated approval of mobocertinib under 21 CFR part 314 subpart H, for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as determined by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

The recommendation for accelerated approval is supported by results from Study AP32788-15-101 (Study 101), an international, open-label, multicohort, dose escalation and dose expansion study. Patients with advanced EGFR exon 20 insertion mutation-positive NSCLC whose disease had progressed on or after platinum-based chemotherapy who received mobocertinib at the recommended phase 2 dose (RP2D) in the primary efficacy population (n=114) had an overall response rate (ORR) of 28% (95% confidence interval [CI] 20, 37) based on blinded independent central review (BICR) with a median duration of response (DOR) of 17.5 months (95% CI 7.4, 20.3). All patients in the primary efficacy population had progressed on prior platinum-based therapy and 42% had received a prior anti-PD-(L)1 antibody. Patients were enrolled at sites distributed across multiple geographic regions (Asia Pacific [China, Japan, other], Europe, and North America, including 53 (46%) patients from the United States, ensuring that the results are largely applicable to the intended U.S. population.

The submitted evidence meets the statutory evidentiary standard for accelerated approval. An ORR of sufficient magnitude and duration is an endpoint reasonably likely to predict clinical benefit in patients with NSCLC, and this endpoint has supported the accelerated approvals of multiple other targeted therapies for patients with NSCLC harboring oncogenic driver mutations (Blumenthal 2015). The lower bound of the 95% confidence interval around the point estimate for ORR observed in the primary efficacy population from Study 101 overlaps with the point estimate for ORR observed with FDA-approved available therapies for this refractory population, irrespective of mutation status, (e.g., 5-23% with docetaxel, docetaxel in combination with ramucirumab). However, mobocertinib's improved median DOR over available single agent chemotherapies (17.5 months vs. approximately 6 months) coupled with ease of administration (once daily oral administration) and differing safety profile, with risk mitigation procedures as described

in product labeling are implemented, provides a meaningful advantage over available therapies.

This is the first approval of an oral targeted therapy for patients with EGFR exon 20 insertion mutation-positive NSCLC and when considered in the context of the route of administration, and its safety profile, the ORR and durable responses observed with mobocertinib are reasonably likely to predict clinical benefit and provide a meaningful advantage over available treatments for this disease.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lung cancer is the leading cause of cancer deaths, accounting for almost 25% of all cancer deaths in 2021 (Siegel 2021). Population-level mortality from NSCLC has declined over the past 10 years, with the reductions in mortality surpassing the reductions in incidence (Sigel 2021, Howlader 2020). Analysis of SEER data suggests that the reduction in mortality from NSCLC accelerated starting in 2013, coinciding with the recommendations for routine testing for EGFR and ALK molecular alterations, with improvements in survival likely related to the identification of oncogenic driver mutations and the development and approval of therapies targeting these mutations (Howlader 2020). Despite these advances, metastatic NSCLC remains a fatal, incurable disease, with a 5-year survival rate of <10%.

EGFR exon 20 insertion mutations occur in ~2-3% of all NSCLC cases and their presence is generally associated with limited response to first- and second-generations EGFR TKIs (Remon 2020, Riess 2018, Oxnard 2013, Arcila 2013). Standard first line treatment in the U.S. for patients with metastatic NSCLC harboring EGFR exon 20 insertion mutations are the same therapies as those used for patients with NSCLC without a specific driver mutation identified, including platinum-based chemotherapy with an immune checkpoint inhibitor (ICI). However, the benefit of ICIs in patients with EGFR exon 20 insertion mutated NSCLC is not well studied (Remon 2020, Remon 2021). Available treatment options for patients who have progressed following platinum-based chemotherapy include ramucurimab plus docetaxel, single agent chemotherapy, or an anti-PD-(L)1 antibody as a single agent for patients who are anti-PD-(L)1 naïve. Amivatamab-vmjw was granted accelerated approval in May 2021 for the treatment of patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy; however, no targeted therapy for the treatment of patients with NSCLC harboring an EGFR exon 20 insertion mutation has been granted regular approval, and no oral targeted therapy has received either accelerated or regular approval.

Mobocertinib is a kinase inhibitor that irreversibly binds to EGFR exon 20 insertion mutations at lower concentrations that wild type EGFR. The proposed dosing regimen is 160 mg orally once daily, with or without food. Takeda's proposed indication for mobocertinib is, "for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, who have progressed on or after [redacted] (b) (4) platinum-based chemotherapy."

The primary efficacy population for this review comprises 114 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations treated with mobocertinib 160 mg orally once daily (QD) in the multi-cohort Study 101. All patients in the primary efficacy population received prior treatment with platinum-based chemotherapy. The primary efficacy outcome measure was ORR assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The confirmed ORR was 28% (95% CI: 20, 37) and the median DOR was 17.5 months (95% CI: 7.4, 20.3). A total of 59% of responders had a DOR ≥6 months and 19% of responders had a DOR ≥ 12 months.

Mobocertinib has an acceptable safety profile when assessed in the context of a life-threatening disease. The safety databases consisted of 256 patients with NSCLC and other solid tumors who received mobocertinib at a dose of 160 mg orally once daily; this included the 114 patients in the primary efficacy population. Among these patients (n=256), the most common (> 20%) adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. Serious adverse reactions occurred in 46% of patients in the primary safety population (n=114); the most common (≥ 2%) were diarrhea, dyspnea, vomiting, pyrexia, acute kidney injury, nausea, pleural effusion, and cardiac failure. Permanent discontinuation of mobocertinib due to adverse reactions occurred in 17% of patients; the most frequent events leading to permanent discontinuation (≥ 2%) were diarrhea and nausea. Fatal adverse reactions occurred in 1.8% of patients, including events of cardiac failure (0.9%), and pneumonitis (0.9%).

Safety issues identified as significant and serious during the NDA review were QTc interval prolongation and Torsades de Pointes, interstitial lung disease (ILD)/pneumonitis, cardiac toxicity, and diarrhea. Due to the life-threatening nature of QTc interval prolongation and Torsades de Pointes, a box warning was included in product labeling in addition to usage, monitoring, and dosage modification guidelines. These risk mitigation measures are considered sufficient for risk management given oncologists' experience with the management of QTc prolongation such that a Risk Evaluation and Management Strategy (REMS) was not considered necessary. All other safety concerns are adequately addressed by information in the Warnings and Precautions section of mobocertinib product labeling and in the dose modification guidelines included in product labeling. Post-marketing requirements will be issued for progression-free survival (PFS) data from a randomized clinical trial of mobocertinib to verify and confirm its benefit in patients with EGFR exon 20 insertion mutated NSCLC and for additional safety data to characterize the risks of QTc prolongation and Torsades de Pointes and cardiac failure. A post-marketing commitment will be issued to characterize the safety and efficacy of mobocertinib in U.S. racial and ethnic minorities including Black/African American patients with NSCLC with EGFR exon 20 insertion mutations, who were underrepresented in the primary efficacy population in Study 101.

An application for Pre-Market Approval (PMA) for the Oncomine Dx Target Test (ODxTT) was submitted to the Center for Devices and Radiological Health (CDRH) for contemporaneous review and approval with this NDA.

Therefore, based on a favorable risk:benefit profile and findings reasonably likely to predict clinical benefit with a meaningful advantage over available therapies, mobocertinib was granted accelerated approval for the following indication:

"Treatment of adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer deaths accounting for almost 25% of all cancer deaths in 2021. (Siegel, 2021) • EGFR exon 20 insertion mutations occur in ~2-3% of all NSCLC cases and their presence is generally associated with limited response to first- and second-generations EGFR TKIs. (Remon 2020, Riess 2018, Oxnard 2013, Arcila 2013) • In the US, the 5-year relative survival rate for NSLC with distant disease is 7% (American Cancer Society, 2021)	Locally advanced/metastatic NSCLC with EGFR exon 20 insertion mutations is a life-threatening disease with poor survival. NSCLC with EGFR exon 20 insertion mutations is a rare subset of NSCLC.
Current Treatment Options	• No therapy has received regular approval specifically for the treatment of patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations. Treatment options for patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations who have progressed on prior therapy are the same as those used for patients with NSCLC without a specific driver mutation, although this effectiveness of these treatments has not specifically studied in this subpopulation.	There is an unmet medical need for patients with previously treated NSCLC harboring EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. This conclusion is based on the observed ORRs, DORs, and overall survival (OS) reported for therapies currently used in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Amivatamab-vmjw, a bispecific antibody that targets EGFR exon 20 insertion mutations, received accelerated approval in May 2021 for the treatment of patients with NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on platinum-based chemotherapy. • For patients with progression of disease following platinum-based chemotherapy, treatment options include chemotherapy (single agent or docetaxel in combination with ramucirumab) associated with ORRs of 6-23% with median DORs in the range of 4-9 months, or single agent anti-PD-(L)1 antibodies if not received in the first-line setting, associated with ORRs of 14-20% and median DORs in the range of 16-17 months.	clinical practice for the treatment of this patient population.
Benefit	• The primary efficacy data supporting this NDA are from patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy enrolled in Study 101, an international, open label, multicohort, dose escalation and dose expansion study in patients with locally advanced or metastatic NSCLC whose disease was refractory to standard available therapies. • Among the 114 patients in the primary efficacy population, the confirmed ORR by BICR was 28% (95% CI 20, 27), the median duration of response (DOR) was 17.5 months (95% CI: 7, 20), and 59% of patients had a DOR ≥ 6 months. The ORRs observed in the subgroups of patients who received prior anti-PD-(L)1 therapy (n=48) and those who did not receive prior anti-PD-(L)1	The submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed ORR, along with the observed duration of responses, are clinically meaningful in the context of the poor prognosis of the disease and the limited available approved therapies. While the lower bound of the 95% CI of the ORR observed in the primary efficacy population did not exceed the point estimate for ORR observed with available therapies (e.g., docetaxel with ramucirumab), the improved duration of response, option for treatment with a single

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	therapy (n=66) were consistent with the primary analysis, at 25% (95% CI 14, 40) and 30% (95% CI 20, 43), respectively. • Information submitted by the Applicant utilizing data from Flatiron Health (TAK-788-5002) reported that amongst patients with NSCLC with EGFR exon 20 insertion mutations 8.5% of treatment-naïve patients and 7% of previously treated patients were Black or African American. In the primary efficacy population of Study 101, a total of 3 patients (3%) were Black or African American and one patient (0.9%) was Hispanic/Latinx.	agent administered orally, and the differing safety profile make this provide a meaningful advantage to patients with an unmet need. When considered in this context, the ORR and durable responses observed with mobocertinib are reasonably likely to predict clinical benefit and provide a meaningful advantage over available therapies. Given the relatively limited duration of follow-up and the number of 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, therefore, additional data to verify the clinical benefit of mobocertinib for patients with NSCLC harboring EGFR exon 20 insertion mutations will be obtained from a randomized clinical trial with a primary endpoint of progression-free survival (PFS). Based on the demographic characteristics of patients with NSCLC with EGFR exon 20 insertion mutations in the U.S.,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		particularly the proportion of Black/African American and Hispanic/Latinx patients with this disease, the primary efficacy population from Study 101underrepresents these racial and ethnic subpopulations. Therefore, additional data to further characterize the safety and efficacy of mobocertinib in Black/African American and other underrepresented racial/ethnic subpopulations with EGFR exon 20 insertion mutated NSCLC will be obtained from ongoing and future clinical trials, as part of a post-marketing commitment.
Risk and Risk Management	• The safety database for this NDA comprises 256 patients with NSCLC and other solid tumors who received mobocertinib 160 mg orally QD, including the 114 patients who also comprise the primary efficacy population. Among these patients, serious adverse reactions occurred in 46% of patients, of which the most common (≥2%) were diarrhea, dyspnea, vomiting, pyrexia, acute kidney injury, nausea, pleural effusion, and cardiac failure. • Fatal adverse reactions occurred in 1.8% of patients, including events of cardiac failure (0.9%) and pneumonitis (0.9%). • Permanent discontinuation occurred in 17% of patients in the primary safety population; the most common (≥2%) adverse	The observed safety profile of mobocertinib is acceptable when assessed in the context of the treatment of a life-threatening disease. Although mobocertinib can cause serious adverse reactions, these safety concerns are adequately addressed by information in the Boxed Warning and the Warnings and Precautions and Dosage and Administration sections of product labeling. Mobocertinib will be prescribed by oncologists who know how to monitor,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	reactions requiring permanent discontinuation of mobocertinib were diarrhea and nausea. • Dosage interruptions of mobocertinib due to an adverse reaction occurred in 51% of patients; the most common (>5%) adverse reactions which required dosage interruption were diarrhea, nausea and vomiting. Dose reductions of mobocertinib due to an adverse reaction occurred in 25% of patients. The only adverse reaction requiring dose reduction in >5% of patients was diarrhea. • Safety issues considered serious and significant enough to warrant inclusion in the Warnings and Precautions section of the USPI were QTc interval prolongation and Torsades de Pointes, interstitial lung disease (ILD)/pneumonitis, cardiac toxicity, and diarrhea. • A significant safety concern that was identified during NDA review was QTc prolongation / Torsades de Pointes. To address this potentially life-threatening or fatal adverse reaction, a Boxed Warning was included in product labeling in addition to usage and dose modification guidelines.	identify, and manage the toxicities described in the USPI; therefore, the risk mitigation strategies included in the label are considered sufficient and a REMS was not considered necessary for the safe use of mobocertinib. In addition, post-marketing requirements will be issued for data from ongoing studies to further characterize the risks of QTc prolongation/Torsades de Pointes and cardiac failure.

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
	□	Clinical outcome assessment (COA) data, such as			
			X	Patient-reported outcome (PRO)	Section 8.1.2.1.7
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Nicole Drezner, M.D.

Cross-Disciplinary Team Leader

2.0 THERAPEUTIC CONTEXT

2.1 Analysis of Condition

The Applicant's Position:

2.1.1 Epidemiology and Pathology

Lung cancer is the most common cancer and leading cause of cancer death globally, representing 11.6% of all cancer diagnoses and 18.4% of total cancer deaths in the world. In the United States (U.S.), an estimated 234,030 new cases of lung and bronchial cancer were diagnosed in 2018, with 154,050 lung cancer–related deaths [1].

Of the 2 main histologic types of lung cancer (small-cell lung cancer and NSCLC), NSCLC represents over 85% of all lung cancers and includes a number of subtypes such as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and bronchioloalveolar carcinoma [2,3]. Most patients with NSCLC present with either locally advanced or metastatic disease, with 70% to 80% of patients presenting with potentially inoperable, later-stage disease, thereby contributing to a 5-year overall survival (OS) rate of approximately 15% to 17% [3,4].

2.1.2 *EGFR Exon 20* Insertion Mutations

In recent years, attention has turned to stratifying patients with lung cancer based on molecular alterations, because it has become clear that histologically identical tumors are driven by different oncogenes and are therefore likely to respond differently to therapeutic intervention. Activating mutations in the *EGFR* gene have been identified in 15% to 40% of patients with NSCLC; up to 50% of patients with adenocarcinoma have *EGFR* mutations [5-9]. In western countries, the prevalence of *EGFR* mutations in lung cancer ranges from 3% to 42% with an average of about 15% and 23% reported across multiple studies in Europe and the U.S., respectively [10]. The most common activating mutations in *EGFR* are in-frame deletions in exon 19 and a Leu858Arg (L858R) substitution in exon 21, which account for about 85% to 90% of all *EGFR* activating mutations [11-13]. In addition, 5% of activating *EGFR* mutations are so called "uncommon" mutations, which include *EGFR* point mutations at amino acids in exons 18, 20, and 21 (eg, G719, S768, and L861, respectively). Furthermore, 4% to 9% of all *EGFR* activating mutations are reported as a diverse family of in-frame insertions in exon 20, sometimes referred to as duplication, that account for ~2% of all NSCLC [11-14]. Studies have shown that adult patients with NSCLC containing *EGFR Exon 20* insertion mutations exhibit clinical characteristics similar to those carrying common *EGFR* mutations, such as higher Asian and female prevalence with no smoking history and predominantly adenocarcinoma histology [12]. On the basis of a large next generation sequencing (NGS) study, approximately 3000 patients are estimated to be diagnosed with NSCLC with the *EGFR Exon 20* insertion mutation annually in the U.S. [15].

The discovery of driver oncogenes like *EGFR* and the subsequent development of targeted TKIs for common and treatment-emergent mutations in *EGFR* in NSCLC have dramatically advanced the treatment paradigm and improved patient outcomes [8,16-19]. Although several EGFR TKIs

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have been approved for the treatment of NSCLC with common mutations, such as in-frame deletions in exon 19 and a L858R substitution in exon 21, resistant T790M mutation, or uncommon mutations, there are no TKIs approved or adequate therapy available for patients with NSCLC with *EGFR* activated by exon 20 insertion mutations. The *EGFR Exon 20* insertion mutations are unique oncogene driver mutations [15] and are now recognized as an independent subclass of *EGFR* mutations with oncogenic properties similar to those observed with the most common *EGFR* mutations. Unlike patients with NSCLC harboring common *EGFR* mutations, patients with NSCLC with *EGFR Exon 20* insertion mutations derive very little benefit from existing therapies [11], therefore constituting an unmet medical need that is being addressed by mobocertinib.

The FDA's Assessment:

FDA generally agrees with Takeda's position. Although EGFR exon 20 insertion mutations are more common in women, non-smokers, and those with adenocarcinoma histology. (Oxnard 2013) and data on the epidemiology and demographic characteristics of patients with NSCLC with EGFR exon 20 insertion mutations is still emerging, a recently published retrospective study of patients with NSCLC in the U.S. showed that patients with EGFR exon 20 insertion mutations were more likely to be Black (14% vs. 6%; $P < 0.001$) or Asian (22% vs. 10%; $P < 0.001$) when compared to other patients with NSCLC (Choudhury 2021). Information submitted by the Applicant utilizing data from Flatiron Health (Study TAK-788-5002) reported that amongst patients with NSCLC with EGFR exon 20 insertion mutations 8.5% of treatment-naïve patients and 7% of previously treated patients were Black or African American. While only limited data are available describing the proportion of Hispanic/Latinx patients with NSCLC with EGFR exon 20 insertion mutations, the proportions of Hispanic/Latinx treatment-naïve and previously treated NSCLC with EGFR exon 20 insertion mutations in Study TAK-788-5002 were 5% and 7%, respectively.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

In the absence of targeted therapies, patients with NSCLC with *EGFR Exon 20* insertion mutations currently are mainly treated by chemotherapy, immunotherapy, or TKIs that are approved for the common *EGFR* mutations. These therapies have limited clinical benefit to patients whose tumors harbor *EGFR Exon 20* insertion mutations, with a poor objective response rate (ORR) and progression-free survival (PFS) [3,11,20-33]. Real world data recently presented at the World Congress on Lung Cancer reported a median PFS in the second-line setting of 3.2 months and a median OS of 13.3 months in patients with NSCLC harboring *EGFR Exon 20* insertion mutations across all available therapeutic options [34]. Table 1 summarizes the clinical efficacy outcomes in patients with previously treated NSCLC from the literature and real-world databases, either as an unselected population or, when available, specifically in *EGFR Exon 20* insertion mutations.

Table 1: Available Therapies for Previously Treated NSCLC (Unselected and *EGFR Exon 20* Insertion Mutations)

						Physician-directed Therapy [h]		
	EGFR TKI	**Immuno-oncology Monotherapy**		**Docetaxel**	**Docetaxel + Ramucirumab [a]**	**Previously Treated**	**Previously Treated, Study 101-Aligned [i]**	**Previously Treated With Platinum-based Chemotherapy, Study 101-Aligned [i]**
Efficacy Endpoint	***EGFR Exon 20***	**Unselected**	***EGFR Exon 20*** [e]	**Unselected**	**Unselected**	***EGFR Exon 20***	***EGFR Exon 20***	***EGFR Exon 20***
ORR, % (n)	~10 [b]	14 [c] to 19 [d]	3.5	5.5 to 14 [f]	23 (144/628) [f]	9.6 (11/114)	11.1 (7/63)	14.0 (7/50)
DCR, %	NR	NR	24 to 30	53 [f]	64 [f]	41.2	47.6	44.0
Median DOR, months	NR	16.3 [c] to 17.2 [d]	NA	5.6 [d] to 6.2 [c]	NR	NA [j]	NA [j]	NA [j]
Median PFS, months	1.4 to 2.7 [b]	2.3 [d] to 2.8 [c]	2.3 to 4.0	2.8 to 4.2 [f]	4.5 [f]	3.7	3.4	3.3
Median OS, months	NR	12.2 [d] to 15.6 [c, g]	7.1 to 8.1	5.7 to 9.6 [f]	10.5 [f]	13.6	13.6	11.5

Source: [3,24-27,33,35-39]; Study TAK-788-5002 CSR; second-line immunotherapy white paper.

CSR: clinical study report; DCR: disease control rate; DOR: duration of response; EGFR: epidermal growth factor receptor; DOR: duration of response; NA: not applicable; NR: not reported; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; TKI: tyrosine kinase inhibitor; U.S.: United States.

[a] Data on the clinical benefit of ramucirumab in combination with docetaxel in treatment of patients with NSCLC with *EGFR Exon 20* insertion mutations are not conclusive due to the limited usage of the combination as a second-line or greater therapy for patients with NSCLC ([40-44] and Applicant review of Flatiron Health electronic medical records (b) (4)

[b] [3].

[c] [26] (N = 425 per group).

[d] [25] (nivolumab, N = 292; docetaxel, N = 290).

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Table 1: Available Therapies for Previously Treated NSCLC (Unselected and *EGFR Exon 20* Insertion Mutations)

						Physician-directed Therapy [h]		
	EGFR TKI	**Immuno-oncology Monotherapy**		**Docetaxel**	**Docetaxel + Ramucirumab [a]**	**Previously Treated**	**Previously Treated, Study 101-Aligned [i]**	**Previously Treated With Platinum-based Chemotherapy, Study 101-Aligned [i]**
Efficacy Endpoint	***EGFR Exon 20***	**Unselected**	***EGFR Exon 20*** [e]	**Unselected**	**Unselected**	***EGFR Exon 20***	***EGFR Exon 20***	***EGFR Exon 20***

[e] White paper "Efficacy of Immunotherapy in Previously Treated Patients With Non-small Cell Lung Cancer With *EGFR* Exon 20 Insertion Mutations" (second-line immunotherapy white paper). The ORR is based on the meta-analysis described in the white paper, and the other efficacy parameters are based on the individual sources described in the white paper.

[f] [24-26,33,35-39] (Docetaxel + ramucirumab, N = 628 in [24]).

[g] [27] Range of OS also includes 12.7 months (N = 60).

[h] TAK-788-5002: Retrospective Observational Study of Non-small Cell Lung Cancer (NSCLC) Patients with *EGFR Exon 20* Insertion Mutations: Real World Data Generation of Natural History. This study used data from Flatiron Health Research Database.

[i] Study 101-aligned patients had baseline characteristics that were aligned with the inclusion/exclusion criteria of Part 3 of Study 101.

[j] DOR results from the real-world setting (Study TAK-788-5002) are NA because of the small number of responders.

The FDA's Assessment:

FDA agrees with the Applicant's description of the available therapies for patients with NSCLC with EGFR exon 20 insertion mutations who have received prior platinum-based chemotherapy, which include ramucurimab plus docetaxel, single agent chemotherapy, or anti-PD-(L)1 antibody as a single agent for patients who were anti-PD-(L)1 naïve. Amivatamab-vmjw was granted accelerated approval in May 2021 for the treatment of patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy; the approval was based on an observed ORR of 40% (95% CI: 29, 51) and a median DOR of 11.1 months (95% CI: 6.9, not estimable [NE]). However, no other oral targeted agent has received accelerated or regular approval for the treatment of patients with NSCLC with EGFR exon 20 insertion mutations.

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2.3 Current Application for Mobocertinib

With this application, the Applicant is seeking approval for mobocertinib as a treatment for patients with *EGFR Exon 20* insertion mutation-positive metastatic non-small cell lung cancer (NSCLC), who have received prior platinum-based chemotherapy.

2.3.1 Mobocertinib (Formerly TAK-788 and AP32788)

Mobocertinib (formerly TAK-788 and AP32788), an oral, first-in-class, irreversible TKI, was uniquely designed to address the limitations of existing therapies targeting EGFR and HER2. An iterative, structure-guided design strategy was used to optimize affinity and selectivity for EGFR with exon 20 insertion mutations over WT EGFR and to thereby differentiate it from available TKIs. Mobocertinib forms a covalent bond with cysteine 797 in EGFR, which results in sustained inhibition of EGFR signaling. The flexible monocyclic core of mobocertinib may contribute to its ability to bind and inhibit *EGFR Exon 20* insertion mutations, which are thought to enhance the stability of the active conformation of EGFR by changing the position of the C-helix, a structural component of EGFR outside the ATP binding pocket [45]. It is predicted that this altered conformation distal to the ATP binding pocket prohibits the efficient binding of the approved EGFR TKIs to *EGFR Exon 20* insertion mutations. Collectively, these features differentiate mobocertinib from the approved EGFR inhibitors: increased potency via high affinity binding and sustained inhibition of EGFR kinase activity in the *EGFR Exon 20* insertion mutations. Based on its unique mechanism of action inhibiting *EGFR Exon 20* insertion mutants more potently than WT EGFR, mobocertinib was predicted to provide therapeutic benefit to patients with NSCLC harboring *EGFR Exon 20* insertion mutations.

2.3.2 Brief Summary of Evidence for the Proposed Indication

Study 101 is a 3 part, global Phase 2, pivotal, single-arm, open-label study designed to evaluate the efficacy and safety of mobocertinib in the treatment of patients with locally advanced or metastatic NSCLC with *EGFR Exon 20* insertion mutations who have been previously treated with at least 1 prior line of therapy for locally advanced or metastatic disease.

Patients, from Study 101, who were previously treated with a platinum-based therapy were pooled for analysis. This pooled prior platinum pretreated set included patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations who had previously been treated with platinum-based chemotherapy from Part 1 (treated at the recommended dose), Expansion Cohort 1 of Part 2, and Part 3. Efficacy results from the 01 November 2020 data cutoff in the Pooled Prior Platinum Analysis Set form the primary basis to support the initial registration of mobocertinib. The submission is primarily based on positive results from this Pooled Prior Platinum Analysis Set of Study 101 (defined in Section 8.1.1.1.4).

Results from individual Parts 1 and 2 (dose-escalation and expansion cohorts) and Part 3 (extension cohort) of Study 101, Part 1 of Study TAK-788-1003, and the analysis of RWD from the historical benchmark study TAK-788-5002 and other relevant RWD sources are included in the submission as supportive evidence.

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The primary endpoint of cORR as assessed by an independent review committee (IRC) for imaging was tested after all patients had an opportunity to complete at least 6 cycles of therapy (data cutoff 29 May 2020). A subsequent efficacy analysis was performed using a data cutoff of 01 November 2020 to allow for additional characterization of the treatment effect of mobocertinib. Efficacy analyses were conducted on the Part 3 full analysis set and the Pooled Prior Platinum Analysis Set.

The FDA's Assessment:

FDA agrees with the Applicant's summary of Study 101 as the primary source of evidence for this NDA.

3.0 REGULATORY BACKGROUND

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Mobocertinib has had an active Investigational New Drug Application (126,721) in the U.S. since January 2016, and is not marketed in any region. Mobocertinib was granted the following designations in the U.S.

- Orphan drug designation was granted on 17 December 2019 for the treatment of NSCLC with genetic alteration in *EGFR* including *EGFR* mutations and/or *EGFR* gene amplification, *HER2* mutations, or BRAF G466V mutations.
- Breakthrough Therapy Designation (BTD) was granted on 23 April 2020 for the treatment of patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations whose disease has progressed on or after platinum-based chemotherapy.
- Fast Track Designation was granted on 03 June 2020 for the treatment of metastatic NSCLC harboring *EGFR Exon 20* insertion mutations.

The FDA's Assessment:

FDA agrees with the Applicant's position.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of regulatory interactions is provided in Table 2

Table 2: Summary of Regulatory Interactions

End-of-Phase 1 meeting 11 June 2018	• The Agency noted that evaluation of the clinical significance of the primary endpoint, ORR, and the adequacy of the data to support an approval would consider the magnitude and duration of the responses in a risk-benefit analysis in the context of available therapy. • The Agency agreed in general with the Applicant's nonclinical plan, clinical pharmacology plan, and the plan for codevelopment of a companion diagnostic to support the initial NDA submission.
End-of-Phase 2 meeting 29 May 2019	An agreement was reached, pending the final results of Study 101, that TAK-788-3001 would be acceptable as a clinical study intended to verify the clinical benefit of mobocertinib for the treatment of patients with *EGFR Exon 20* insertion mutation-positive NSCLC.
Type C FDA Written Responses 03 June 2020	The Agency provided guidance and feedback on proposed analysis plans for the integrated safety, integrated efficacy, datasets, population PK, concentration-corrected QT interval (QTc), exposure-response, and physiologically-based PK analyses.

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Table 2: Summary of Regulatory Interactions

Type B Multi-disciplinary BTD meeting 10 August 2020	The Agency advised that the primary efficacy analysis for the NDA should be conducted in the Pooled Prior Platinum Analysis Set across all parts of Study 101.
Pre-NDA Meeting 10 November 2020	• The Agency agreed to the Applicant's proposed plan to submit the initial NDA in February 2021 primarily based on efficacy data from the November 2020 data cutoff and safety results from May 2020 data cutoff in Study 101. • The Agency also recommended to include an early futility analysis to the ongoing Study TAK-788-3001 due to preliminary emerging data in the treatment-naïve cohort with mobocertinib monotherapy from Study 101. The Agency recommended evaluation of mobocertinib in combination with chemotherapy in the treatment-naïve setting and that the plan for the combination study should be discussed with the Agency by the time of the initial NDA submission in February 2021.
Type B meeting February 2021	The Agency provided feedback on the design of the proposed combination study for mobocertinib and chemotherapy, Study TAK-788-3002.
Type B CMC & Clinical Pharmacology FDA meeting March, July, and December 2020	Applicant and the Agency aligned in March 2020 and July 2020, respectively, on preparation of the key components of the planned chemistry, manufacturing, and controls (CMC) activities and the registration package for the planned NDA submission; feedback was received in December 2020 regarding the planned assessment of comparability between drug products.
iPSP for full waiver of pediatric studies, agreed by the Agency on 29 May 2020	Mobocertinib received a full waiver of pediatric studies for the treatment of NSCLC and advanced solid tumors that harbor an *EGFR*/*HER2* mutation across all pediatric age groups. The agreed initial pediatric study plan is included in the original NDA submission per 505B(a)(3)(A)(ii)(II) of the Food, Drug, and Cosmetic Act.
Companion Diagnostic March 2019	The Applicant partnered with Thermo Fisher Scientific to codevelop Oncomine Dx Target Test as a companion diagnostic for mobocertinib. A presubmission meeting with the Center for Devices and Radiological Health (CDRH) at FDA was held in March 2019 (see FDA CDRH Presubmission Minutes). Thermo Fisher plans to submit a supplemental premarket approval application to seek concurrent approval of Oncomine Dx Target Test.

CDRH: Center for Devices and Radiological Health; CMC: chemistry, manufacturing, and controls; iPSP: Initial Pediatric Study Plan; NDA: New Drug Application; NSCLC: non-small cell lung cancer; PK: pharmacokinetic; QTc: concentration-corrected QT interval

The FDA's Assessment:

FDA agrees with the Applicant's position. During the pre-NDA meeting on November 10, 2020, FDA recommended that the Applicant consider investigating mobocertinib in combination with standard of care first-line therapy (e.g., platinum-based chemotherapy) and suggested that a more appropriate control for Study TAK-788-3001 would be platinum-based chemotherapy plus an anti-PD(L)1 antibody given that although the benefit of anti-PD-(L)1 agents specifically for the treatment for patients with EGFR exon 20 insertion mutations has not been well characterized, there are small case studies suggesting that these patients may respond favorably to anti-PD-(L)1

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antibodies, in contrast to the more common EGFR mutations (Negrao 2018, Lau 2021). In the Type B meeting held in February 2021, FDA reiterated that in the U.S., the standard of care for first-line treatment of metastatic NSCLC with EGFR exon 20 insertion mutations is the same as for patients with metastatic NSCLC without an oncogenic driver mutation, e.g., an anti-PD-(L)1 antibody alone or in combination with chemotherapy.

In addition, during the pre-NDA meeting in November 2020, FDA expressed concern about emerging data describing the antitumor activity of mobocertinib as a single agent for the first-line treatment of patients with EGFR exon 20 insertion mutations, with observed ORRs that were lower than those observed with standard first-line therapy for NSCLC. In light of this data, FDA strongly recommended that an early futility analysis be implemented in Study TAK-788-3001.

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4.0 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

[FDA completes Section 4]

4.1 Office of Scientific Investigations (OSI)

FDA performed clinical inspections of two US clinical sites, Site #58248 (Principal Investigator [PI]: Dr. Lyudmila Bazhenova) and Site #58008 (PI: Dr. Pasi Janne), (b) (4) Sites outside the US were not inspected due to travel restrictions related to the COVID-19 pandemic. The inspections revealed no significant findings at the clinical sites and the CRO site. Based on the results of these inspections, Study 101 appears to have been conducted adequately and the data generated by the inspected clinical investigators (b) (4) appear reliable.

For additional details, see the Clinical Inspection Summary by Lee Pai-Scherf, MD.

4.2 Product Quality

The mobocertinib capsule for oral administration contains 40 mg mobocertinib equivalent to 48.06 mg mobocertinib succinate with no inactive ingredients. The Office of Pharmaceutical Quality (OPQ) assessed NDA 215310 with respect to Chemistry, Manufacturing, and Controls (CMC) and determined that it meets all applicable standards to support the identity, strength, quality, and purity. As such, OPQ recommends approval of this NDA from a quality perspective. An expiration dating period of 24 months may be granted when stored at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) (See USP Controlled Room Temperature).

4.3 Clinical Microbiology

Not applicable.

4.4 Devices and Companion Diagnostic Issues

In Study 101, central determination of EGFR exon 20 insertion mutations was performed using local laboratory tests (LLTs), which are PCR-based and next generation sequencing-based. An application for Pre-Market Approval (PMA; submission P160045/S029) for the Oncomine Dx Target Test (ODxTT) was submitted to the Center for Devices and Radiological Health (CDRH) on May 4, 2021. The application will be approved contemporaneously and includes results from a bridging study from the LLTs to the ODxTT. Analytical validation studies were also submitted to support robust detection of EGFR exon 20 insertion mutations using the ODxT Test. For further details, see the PMA review by Dr. Rama Kamesh Bikkavilli.

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5.0 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1 Executive Summary

Mobocertinib (TAK-788) is an orally active irreversible inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), which was designed to selectively inhibit EGFR exon 20 insertion mutations more potently than wild-type (WT) EGFR. Mobocertinib also inhibits EGFR with common activating mutations (exon 19 deletions and the exon 21 L858R substitution), the primary treatment-emergent resistance mutation T790M, and several uncommon activating mutations. The established pharmacological class for mobocertinib is kinase inhibitor. Genetic alterations in EGFR or HER2 can lead to their aberrant activation, resulting in increased stimulation of downstream signaling pathways and dysregulation of cellular processes such as DNA synthesis and cellular proliferation, thereby promoting tumor development (Arteaga & Engelman, 2014).

Mobocertinib irreversibly binds to EGFR via a covalent bond, leading to inhibition of downstream EGFR signaling. In in vitro biochemical kinase inhibition screening assays, mobocertinib inhibited all 14 members of the EGFR family tested (EGFR, HER2, HER4, and 11 EGFR variants with activating or resistance mutations) and B-lymphoid tyrosine kinase (BLK) at half maximal inhibitory concentrations (IC_{50}) < 1.4 nM. These IC_{50} concentrations were in the range of those achieved clinically at the recommended clinical dose of 160 mg mobocertinib (free C_{max} at the 160 mg clinical dose is approximately 1.2 nM based on ~99% protein binding). There are two pharmacologically active metabolites of mobocertinib, AP32914 and AP32960. The inhibitory activity of these metabolites was similar to that of mobocertinib, with IC_{50} values generally within 2-fold for all kinases tested. Mobocertinib also inhibited Janus kinase 3 (JAK3) and TXK at clinically relevant concentrations based on the combined free C_{max} of mobocertinib, AP32914, and AP32960 (approximately 2 nM) at the 160 mg clinical dose.

In cellular assays, mobocertinib inhibited the in vitro activity of all 14 mutant variants of EGFR (IC_{50} = 2.4–22 nM) at lower concentrations than WT EGFR (IC_{50} = 35 nM). The inhibited variants included four containing a common activating mutation with or without a T790M resistance mutation, five containing an uncommon activating mutation, and five containing an exon 20 activating insertion (IC_{50} = 3.5–23 nM). The cellular activity of metabolites AP32914 and AP32960 was similar to that of mobocertinib, with IC_{50} values generally within 2-fold for both WT and mutant EGFR. The Applicant also evaluated the cellular activity of mobocertinib in NSCLC cell lines harboring EGFR mutations. In a patient-derived NSCLC cell line harboring the EGFR exon 20 NPH insertion mutant, mobocertinib inhibited in vitro cell survival at lower concentrations than WT EGFR (IC_{50} = 21 and 35 nM, respectively). Mobocertinib also inhibited EGFR-mediated signaling in three NSCLC cell lines expressing common EGFR-activating mutations, with or without the T790M resistance mutation. These studies support the proposed mechanism of action of mobocertinib and its activity in the proposed patient population.

The in vivo activity of mobocertinib was evaluated in immunocompromised mice implanted with

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tumors consisting of the following three cell lines: 1) LU0387 cells, a patient-derived xenograft (PDX) model expressing EGFR with an exon 20 NPH activating insertion mutation; 2) Ba/F3 cells engineered to express EGFR with an exon 20 ASV activating insertion mutation; or 3) H1975 NSCLC cells expressing EGFR with an L858R activating mutation plus the T790M resistance mutation. Daily oral administration of mobocertinib led to tumor growth inhibition (TGI) in all three models, with increased efficacy associated with increased plasma concentrations of mobocertinib and its active metabolites, AP32914 and AP32960. Plasma levels of metabolite AP32914 were generally lower and levels of AP32960 were higher than those of mobocertinib. Tumor regression induced by mobocertinib was associated with inhibition of EGFR signaling. Mobocertinib also exhibited in vivo anti-tumor activity in four HER2-driven tumor models.

Secondary pharmacology studies showed that the concentration of mobocertinib required to inhibit the growth of KRAS, ALK, MET, PDGFR, and BRAF mutant NSCLC cell lines in cell growth assays was 2- to 206-fold higher than the concentration required to inhibit WT EGFR activity, suggesting selectivity for EGFR- and HER2-driven cancer cells. Mobocertinib and its metabolites AP32914 and AP32960 inhibited the human ether-a-go-go related gene (hERG) current at concentrations > 5 μM, suggesting a low potential for QT prolongation. Additionally, the in vivo assessments included in the toxicology studies in dogs did not show QT prolongation or any other cardiac electrophysiologic effects, although QT prolongation, including resultant life-threatening arrhythmias, occurred in patients treated with mobocertinib. The reason for the discrepancy between the nonclinical and clinical QT data is unknown. Following single oral administration, $^{[14C]}$mobocertinib-derived radioactivity distributed widely to rat tissues including the liver, adrenal gland, kidney, alimentary canal, uveal tract, and thyroid but brain penetration was low.

There were no unique human metabolites detected in vitro in hepatic microsomes or hepatocytes. In human hepatocytes, the only metabolite observed was AP32960, which was also the major metabolite in the nonclinical species tested. The pharmacologically active metabolites AP32914 and AP32960 were detectable in humans in the clinic. To provide safety coverage, plasma concentrations of AP32960 and AP32914 were assessed in rat and dog GLP-compliant toxicology studies. Plasma levels of these metabolites were present at reasonably similar levels in animals and humans. AP32914 and AP32960 did not inhibit in vitro hERG potassium currents at relevant concentrations or exhibit substantial off-target activity in pharmacology screens. Based on these findings, no further toxicological assessment of these metabolites is warranted at this time.

The Applicant evaluated the toxicity profile of mobocertinib in Sprague-Dawley rats and Beagle dogs in GLP-compliant studies with treatment durations up to 3 months. Findings in one or both species consistent with clinical experience included effects on the pancreas (increased amylase), liver (elevated alanine aminotransferase [ALT], aspartate transaminase [AST]), skin (erosion/ulceration, red and/or dry; histological findings of hyperplasia and inflammation), oral

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cavity (ulceration), and gastrointestinal (GI) system (diarrhea, emesis, decreased food consumption, body weight loss; histological findings of atrophy, single cell necrosis, and mononuclear cell infiltration). Additional target organs in both species included the reproductive system (atrophy and single cell necrosis), lymph nodes (increased lymphoid cellularity), digestive tract (decreased epithelial thickness), eyes (atrophy of the corneal epithelium), and larynx (decreased epithelial thickness).

Other findings in rats included salivary gland acinar atrophy and exacerbation of chronic progressive nephropathy in the kidneys of males. In dogs, treatment with 1 mg/kg mobocertinib (approximately 0.7 times the human exposure by AUC of 951 ng*hr/mL at the 160 mg once daily clinical dose) was not tolerated in males, with clinical toxicity (ulceration of the oral cavity) leading to early euthanasia 10 days prior to scheduled termination. The mobocertinib parent drug AUC of 951 ng*hr/mL was used for nonclinical toxicity comparisons because the parent drug concentration is proportional to that of the two active metabolites in humans. In addition, one male dog at the 1 mg/kg high dose level was euthanized on Day 70 due to poor clinical condition associated with spontaneous botryoid rhabdomyosarcoma in the urinary bladder. Botryoid rhabdomyosarcoma of the canine urinary bladder is a rare tumor with an incidence of less than 0.5% (Gerber & Rees, 2009; Kelly, 1973). The Applicant suggests that this finding was unrelated to mobocertinib, as the dog had hematuria (blood in urine concurrent with the presence of red blood cells microscopically observed in the urine sediment) pre-treatment, and this condition has been previously reported in young dogs. Although this malignancy occurred at the high dose level, given that symptoms of bladder cancer were present in this dog pre-treatment, the FDA agrees that this finding is unlikely to be related to mobocertinib. There were also mobocertinib-related effects on the oral cavity/hard palate (erosion, ulceration and/or inflammation) at tolerated doses, as well as ocular changes including red eyeball/discharge, corneal opacity, and conjunctival hyperemia at exposures ≥ 0.2 times the human exposure at the 160 mg clinical dose. Stomatitis including mouth ulceration has been seen clinically. Additional ocular findings in 4-week toxicology studies included decreased corneal epithelial thickness in rats and sclera injection, partial or complete closure of the eye, and corneal epithelial atrophy in dogs.

Mobocertinib 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. Mobocertinib was not clastogenic in an in vivo bone marrow micronucleus test in rats. It also did not demonstrate phototoxic potential in a GLP-compliant in vitro assay with mouse fibroblasts.

The Applicant did not conduct carcinogenicity or fertility studies with mobocertinib; consistent with ICH S9, these studies are not warranted for the development of a drug intended for the treatment of patients with advanced cancer. The Applicant did assess reproductive organs in the general toxicology studies. The findings included decreases in organ weights affecting multiple reproductive organs including the ovaries, seminal vesicle/prostate gland, and/or uterus at exposures ≥ 0.3 times the human exposure at the 160 mg clinical dose, as well as microscopic

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changes of decreased epithelial thickness/inflammation of the cervix/vagina and atrophy of the uterus, prostate gland, or mammary gland (males only) in rats and/or dogs at exposures ≥ 0.2 times the human exposure at the 160 mg clinical dose.

To address the potential reproductive effects of mobocertinib, the Applicant conducted a GLP-compliant embryo-fetal development study in rats. There was no evidence of embryo-fetal loss at doses up to 5 mg/kg (approximately 0.8 times the clinical AUC at the 160 mg human dose); however, once daily oral administration of 10 mg/kg mobocertinib (approximately 1.7 times the clinical AUC at the 160 mg human dose) to pregnant rats during the period of organogenesis (gestation Days 6 to 20) resulted in adverse effects on embryo-fetal development including embryo-fetal death (increased post-implantation/early resorptions) and decreased fetal weight. This was accompanied by maternal toxicity characterized by a decrease in food consumption and body weight throughout the dosing period. There was no clear evidence of dose-related teratogenicity. The pharmacology/toxicology team recommends a warning in the label for embryo-fetal toxicity. In addition, consistent with current recommendations for non-genotoxic compounds with embryo-fetal lethality described in the FDA Guidance for Industry Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations, and considering the mobocertinib half-life of ~18 hours, the FDA recommends advising males of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week following the last dose. Given that the FDA clinical pharmacology team identified mobocertinib to be a CYP3A inducer, which may compromise the efficacy of hormonal contraception, the FDA recommends advising females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose to account for the total duration of potential CYP3A induction after the final dose. Because of the potential adverse effects of EXKIVITY on a breastfeeding child, product labeling advises patients not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of mobocertinib for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:

This is the initial NDA submission for TAK-788.

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5.3 Pharmacology

5.3.1 Primary Pharmacology

The FDA's Assessment:

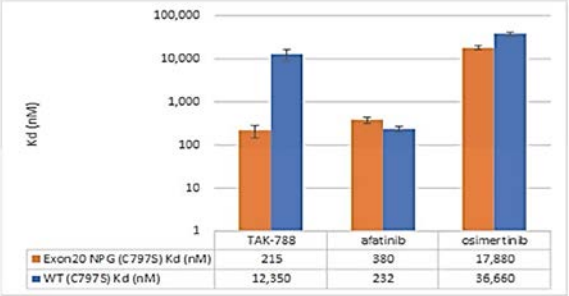
Dr. Dubravka Kufrin reviewed several of the primary pharmacology studies for mobocertinib under the original IND submission. Studies reviewed by Dr. Kufrin are indicated, and the other pharmacology studies were reviewed by Dr. Kelie Reece under the NDA.

A. In Vitro Studies

The Applicant used liquid chromatography–mass spectrometry to confirm that mobocertinib forms an irreversible covalent 1:1 complex with WT EGFR and the EGFR exon 20 D770_N771insNPG (Exon 20 NPG EGFR) insertion mutant (Study ARP550; reviewed by Dr. Kufrin).

The Applicant used surface plasmon resonance to assess the binding of mobocertinib to WT EGFR and the EGFR NPG exon 20 insertion mutant, with osimertinib and afatinib (approved EGFR inhibitors) used as comparators (Study TKD-BCS-00800). Mobocertinib bound to Exon 20 NPG EGFR with a Kd value of 215 nM, but showed reduced binding to WT EGFR (Kd = 12,350 nM). Afatinib exhibited high binding affinity for both Exon 20 NPG EGFR (Kd = 380 nM) and WT type EGFR (Kd = 232 nM). Osimertinib weakly bound both Exon 20 NPG EGFR (Kd = 17,880 nM) and WT EGFR (Kd = 36,660 nM). These data suggest that mobocertinib is more selective for Exon 20 NPG EGFR than WT EGFR (Figure 1).

Figure 1: Binding Affinities for WT EGFR and Exon 20 NPG EGFR Insertion Mutant



Error bars represent the standard deviation of the mean.
EGFR: epidermal growth factor receptor; Kd: equilibrium constant of dissociation; nM: nanomolar (10^{-9} l
WT: wild type.

TAK-788 = Mobocertinib; (Excerpted from the Applicant's submission: Study TKD-BCS-00800)

The Applicant used an in vitro kinase screen to evaluate the activity of mobocertinib against 490 protein kinases, including 372 unique human kinases and 118 mutant variants (Study ARP549; reviewed by Dr. Kufrin). At a concentration of 1 mM, mobocertinib inhibited 28 of the 490 kinases by >50%, including all 14 members of the EGFR family tested (EGFR, HER2, HER4, and 11 EGFR variants with activating or resistance mutations), all 8 additional kinases with a

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cysteine in the position homologous to Cys797 of EGFR, and 6 other kinases. As a note, the activity of mobocertinib against the exon 20 NPG EGFR insertion mutant (shown in Figure 5.a) was not tested in this assay. Investigators conducted a second screen of 38 kinases, which included the 28 kinases inhibited most strongly in the first assay and 10 additional kinases of interest involved in important cellular processes. In this screening assay, multiple concentrations of mobocertinib, as well as its metabolites AP32914 and AP32960, were tested to allow determination of IC_{50} values (Table 3). Of the 28 kinases most strongly inhibited in the first screen, 15 kinases were inhibited with IC_{50} values < 2 nM, including all 14 members of the EGFR family and BLK. These IC_{50} concentrations were in the range of those achieved clinically at the 160 mg dose level of mobocertinib (free C_{max} at the 160 mg clinical dose is approximately 1.2 nM based on ~99% protein binding). Two additional kinases (JAK3 and TXK) were inhibited with IC_{50} values of ~2 nM, four additional kinases (Bruton's tyrosine kinase [BTK], BTK [E41K], bone marrow kinase on chromosome X [BMX], activated CDC42 kinase 1 [ACK1]) were inhibited with IC_{50} values < 20 nM, and the remainder of the 28 kinases (7 kinases) were inhibited with IC_{50} values between 39 nM and 1075 nM. The IC_{50} values of the 10 additional kinases of interest were all ≥8 μM. The kinase inhibitory activity of AP32914 and AP32960 was similar to that of mobocertinib, with IC_{50} values generally within 2-fold for all 38 kinases tested.

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Table 3: In Vitro Inhibition (IC_{50} [nM]) of Human Kinases by Mobocertinib (AP32788) and Metabolites AP32914 and AP32960

Kinase:	AP32788	AP32914	AP32960
ERBB4/HER4	0.1	0.2	0.4
BLK	0.2	0.3	0.6
EGFR	0.2	0.2	0.5
EGFR (L858R, T790M)	0.3	0.2	0.4
EGFR (L858R)	0.3	0.4	0.5
EGFR (L861Q)	0.4	0.3	0.4
EGFR (d752-759)	0.4	0.2	0.8
ERBB2/HER2	0.4	0.3	0.4
EGFR (d747-749/A750P)	0.5	0.5	0.8
EGFR (T790M)	0.7	0.7	1.5
EGFR (d746-750/T790M)	0.8	0.7	1.5
EGFR (G719C)	0.9	0.7	2.6
EGFR (G719S)	0.9	0.7	2.1
EGFR (d747-752/P753S)	1.1	1.4	2
EGFR (d746-750)	1.4	1.8	2.6
JAK3	2.2	3	13.4
TXK	2.3	2.3	5.7
BTK	2.8	1.9	14.9
BTK (E41K)	7.3	6.9	24.6
BMX/ETK	11	6	34
ACK1	15	15	25
TEC	39	16	99
ABL1 (F317I)	49	10	47
ITK	55	16	253
FRK/PTK5	91	31	81
BRK	212	195	395
ALK (L1196M)	272	211	213
LYN	1075	900	1226
LCK	7999	5564	12910
IR	8089	3586	13870
IGF1R	27980	19940	21720
Aurora A	>10000	>10000	>10000
Aurora B	>10000	>10000	>10000
Aurora C	>10000	>10000	>10000
CDK1/cyclin A	>10000	>10000	>10000
CDK2/cyclin E	>10000	>10000	>10000
CHK1	>10000	>10000	>10000
KDR/VEGFR2	>10000	>10000	>10000

(Excerpted from the Applicant's submission: Study ARP549)

The Applicant assessed the inhibitory activity of mobocertinib against WT and mutant EGFR in in vitro cellular assays using Ba/F3 cell lines engineered to express 14 different mutant variants of EGFR and A431 cells that overexpress WT EGFR (Study ARP553; reviewed by Dr. Kufrin). Mobocertinib inhibited the activity of all 14 mutant variants of EGFR (IC_{50} = 2.3–23 nM) at lower concentrations than WT EGFR (IC_{50} = 35 nM) (Table 4: Cellular Inhibitory Activity of Mobocertinib (A32788) and Metabolites AP32914 and AP32960 against WT and Mutant EGFR), although the effects on mutant and WT EGFR were not assessed in the same cell line. The EGFR variants included four containing a common activating mutation (exon 19 deletion or an L858R exon 21 mutation) with or without a T790M resistance mutation (IC_{50} = 2.3–21 nM), five containing an uncommon activating mutation (G719A, G719S, S768I, L861Q, and L861R; IC_{50} = 3.5–20 nM), and five containing an exon 20 activating insertion mutation (A763_Y764insFQEA [FQEA], NPG, V769_D770insASV [ASV], H773_V774 insNPH [NPH], and D770_N771insSVD [SVD]; IC_{50} = 3.5–23 nM). The cellular activity of metabolites AP32914 and AP32960 was similar to that of mobocertinib, with IC_{50} values generally within 2-fold for both WT and mutant EGFR.

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Table 4: Cellular Inhibitory Activity of Mobocertinib (A32788) and Metabolites AP32914 and AP32960 against WT and Mutant EGFR

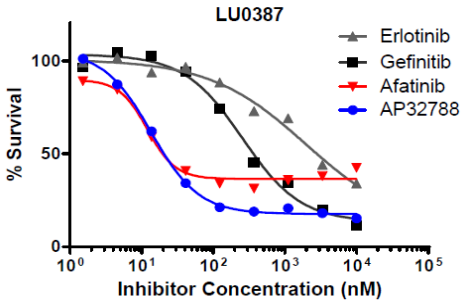
	A431	Common		Common +T790M		Uncommon					Exon 20 Insertion				
Inhibitor	**WT**	**D**	**L**	**DT**	**LT**	**G719A**	**G719S**	**S768I**	**L861Q**	**L861R**	**FQEA**	**NPG**	**ASV**	**NPH**	**SVD**
AP32788	35 ±14 N=4	2.3 ±1.2 N=2	3.0 ±0.1 N=2	6.5 ±1.7 N=11	21 ±12 N=9	18 ±3 N=2	9.3 ±0.2 N=2	20 ±6 N=2	5.2 ±2.4 N=2	3.5 ±1.3 N=2	9.5 ±0.3 N=2	3.5 ±0.6 N=8	8.6 ±2.6 N=8	18 ±4 N=6	23 ±9 N=6
AP32914	22 ±14 N=4	2.2 ±0.9 N=2	2.0 ±1.5 N=2	2.9 ±0.4 N=5	11 ±1 N=9	6.8 ±1.2 N=2	2.9 ±0.6 N=2	15 ±4 N=2	3.4 ±1.3 N=2	2.9 ±0.6 N=2	6.4 ±0.2 N=2	<2.4 N=2	3.8 ±0.6 N=4	11 ±4 N=6	14 ±3 N=6
AP32960	51 ±42 N=6	2.8 ±0.5 N=2	3.1 ±0.6 N=2	11 ±2 N=8	34 ±5 N=7	27 ±1 N=2	13 ±1 N=2	42 ±12 N=2	11 ±3 N=2	6.7 ±0.2 N=2	13 ±2 N=2	7.1 ±2.8 N=5	13 ±3 N=5	32 ±10 N=4	41 ±5 N=4

For highly active compounds (IC_{50}<2.4 nM), an extended dilution series was used (see Section 2.4.2), and <2.4 indicates that an extended curve was not analyzed.

D: Exon 19 E746-A750 del; L: Exon 21 L858R; DT: Exon 19, Exon 20, E746-A750 del, T790M; LT: Exon 21, Exon 20 L858R, T790M
(Excerpted from the Applicant's submission: Study ARP553)

The Applicant evaluated the cellular activity of mobocertinib in NSCLC cell lines harboring EGFR mutations, with erlotinib, gefitinib, and afatinib used as comparators. Investigators assessed the inhibitory activity of mobocertinib against an EGFR exon 20 NPH insertion mutant by evaluating its effect on the viability of a patient-derived NSCLC cell line harboring this mutation (LU0387 cells; Studies ARP554 and TKD-BCS-00756-R1). Mobocertinib inhibited the in vitro survival of NPH mutant LU0387 cells with a slightly lower IC_{50} value (21 nM) than that of A431 cells expressing WT EGFR (IC_{50} = 35 nM; (Figure 2).

Figure 2: Inhibition of LU0387 Cell Survival by Mobocertinib (A32788) and other EGFR Inhibitors



(Excerpted from the Applicant's submission: Study ARP554)

Mobocertinib also inhibited in vitro viability (Table 5), EGFR phosphorylation, and downstream EGFR signaling (Figure 3) in three NSCLC cell lines expressing common EGFR-activating mutations alone (exon 19 deletion [HCC827 cells], L858R exon 21 mutation [H4011 cells]) or with the T790M resistance mutation (L858R/T790M; H1975 cells) (Study ARP554).

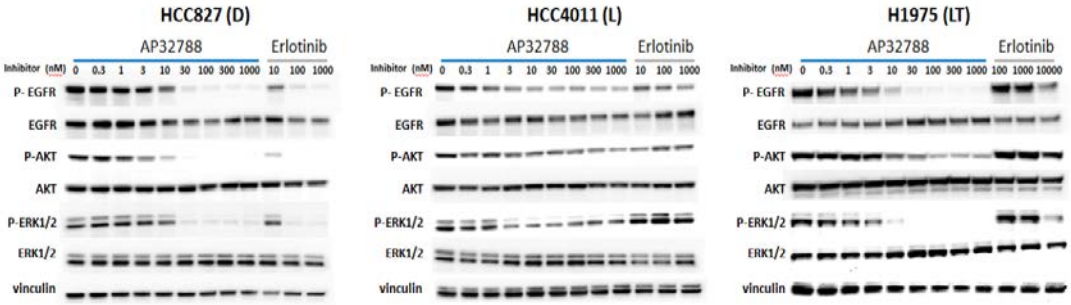
Table 5: Inhibitory Activity of Mobocertinib (A32788) and Other EGFR Inhibitors Against WT and Three EGFR Mutant Variants in NSCLC Cell Lines

	A431	HCC827	HCC4011	H1975
Inhibitors	**WT**	**D**	**L**	**LT**
Erlotinib	71 ±54 N=7	6.7 ±3.6 N=2	17 ±2 N=2	245 N=1
Gefitinib	56 ±38 N=7	4.1 ±2.9 N=2	11 ±1 N=2	2560 N=1
Afatinib	3.9 ±.1.3 N=26	1.4 ±0.5 N=2	0.3 ±0.0 N=2	8.9 ±3.4 N=5
AP32788	35 ±18 N=22	4.0 ±2.2 N=2	1.3 ±0.4 N=2	9.8 ±5.4 N=9

Mutants with IC_{50}s > that of WT EGFR for each TKI are shaded in grey.

D: Exon 19 E746-A750 del; L: Exon 21 L858R; LT: Exon 21, Exon 20 L858R, T790M
(Excerpted from the Applicant's submission: Study ARP554)

Figure 3: Inhibition of EGFR-Mediated Signaling in NSCLC Cell Lines by Mobocertinib (AP32788) and Erlotinib



(Excerpted from the Applicant's submission: Study ARP554)

The Applicant also assessed the in vitro inhibitory activity of mobocertinib against six oncogenic HER2 mutant variants (YVMA, GSP, G776>VC, G776V, V777L, and L755S) using engineered Ba/F3 cells compared to A431 cells overexpressing WT EGFR (Study ARP558; reviewed by Dr. Kufrin). Mobocertinib inhibited all six HER2 mutations with lower IC_{50} values (<2.4–26 nM) than WT EGFR (IC_{50} = 35 nM). The cellular activity of metabolites AP32914 and AP32960 was similar to that of mobocertinib, with IC_{50} values generally within 2-fold for all six mutants.

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

The Applicant investigated the in vivo anti-tumor activity of mobocertinib in immunocompromised mice (10/group) implanted subcutaneously (SC) with patient-derived NSCLC LU0387 tumor fragments expressing an EGFR exon 20 NPH insertion mutation (Study ARP555; reviewed by Dr. Kufrin). When the mean tumor volume was ~150 mm^3, mice were treated with vehicle, mobocertinib (10, 30, or 50 mg/kg), or erlotinib (50 mg/kg) once daily for 21 days (dosing was terminated after 7 days in the 50 mg/kg groups due to >10% body weight loss). Daily oral administration of 10 and 30 mg/kg mobocertinib resulted in 56% and 87% TGI, respectively (Figure 4, top panel), corresponding with total plasma concentrations of 31 and 117 ng/mL at 2 hours post-dose and 8.2 and 55 ng/mL at 6 hours post-dose. Increased anti-tumor

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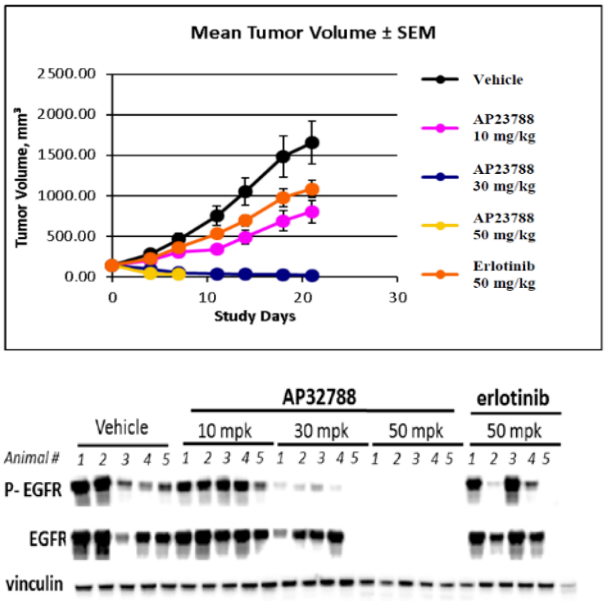
activity was associated with increased plasma levels of mobocertinib and its metabolites. Plasma levels of metabolite AP32914 were generally 3- to 5-fold lower and levels of AP32960 were generally 3- to 4-fold higher than those of mobocertinib. Significant toxicity was not observed based on mortality or body weight at dose levels ≤ 30 mg/kg. At 50 mg/kg, erlotinib induced 38% TGI. Oral administration of 30 mg/kg mobocertinib strongly inhibited EGFR phosphorylation (Figure 4, bottom panel).

Figure 4: Effects of Mobocertinib on In Vivo Tumor Growth and EGFR Signaling in an EGFR Exon 20 NPH Activating Insertion Mutation-Driven NSCLC PDX Model



Numbers 1–5 represent the animal numbers
(Excerpted from the Applicant's submission Study ARP555)

The Applicant investigated the in vivo anti-tumor activity of mobocertinib in immunocompromised mice (10/group) implanted SC with Ba/F3 cells engineered to express an EGFR exon 20 ASV activating insertion mutant (V769_D770insASV) (Study ARP556). When the mean tumor volume was ~150 mm^3, mice were treated with vehicle or mobocertinib (30, 50, or 100 mg/kg) once daily for 7 days. Daily oral administration of 30 mg/kg mobocertinib resulted in 77% TGI, and doses of 50 and 100 mg/kg led to 19% and 90% tumor regression, respectively (Figure 5). There were no mortalities and body weight decreased by ≤7.8% in the 100 mg/kg group compared to controls. Total plasma levels of mobocertinib at 30, 50, and 100 mg/kg were 156, 336, and 811 ng/mL at 2 hours post-dose, respectively, which decreased to 3.5, 18, and 191 ng/mL by 24 hours. Plasma levels of metabolite AP32914 were generally 3- to 11-fold lower and levels of metabolite AP32960 were generally 2- to 5-fold higher than those of mobocertinib.

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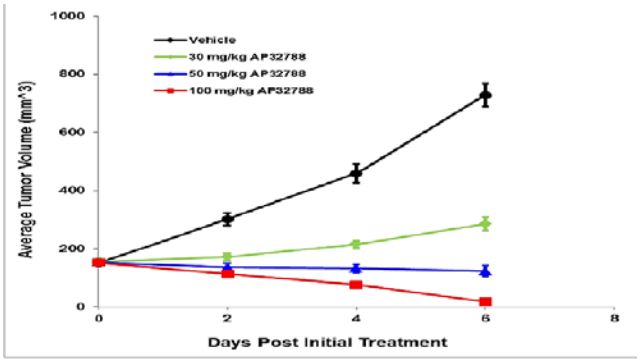
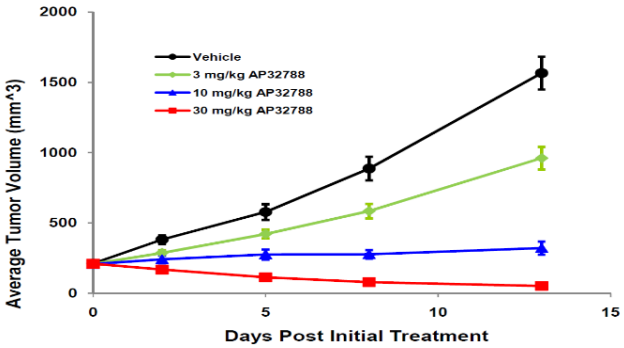
Figure 5: In Vivo Anti-Tumor Activity of Mobocertinib Against an EGFR Exon 20 ASV Activating Insertion Mutation-Driven Ba/F3 Xenograft Model



(Excerpted from the Applicant's submission Study ARP556)

The Applicant investigated the in vivo anti-tumor activity of mobocertinib in immunocompromised mice (10/group) implanted SC with H1975 NSCLC cells that express an EGFR L858R 21 activation mutation plus a T790M resistance mutation (Study ARP557). When the mean tumor volume was ~210 mm^3, mice were treated with vehicle or mobocertinib (3, 10, or 30 mg/kg) once daily for 14 days. Daily oral administration of 3 and 10 mg/kg mobocertinib resulted in 44% and 92% TGI, and 30 mg/kg induced 76% tumor regression (Figure 6). There were no mortalities and only slight decreases in body weight (≤3.5%). Total plasma levels of mobocertinib at 3, 10, and 30 mg/kg were 11, 43, and 191 ng/mL at 2 hours post-dose, respectively, and were undetectable by 24 hours. Plasma levels of metabolite AP32914 were generally 2- to 4-fold lower and levels of metabolite AP32960 were generally 2-fold higher than those of mobocertinib.

Figure 6: In Vivo Anti-Tumor Activity of Mobocertinib in NSCLC Xenografts Expressing an EGFR L858R 21 activation mutation plus T790M resistance mutation



(Excerpted from the Applicant's submission Study ARP557)

The Applicant investigated the in vivo anti-tumor activity of mobocertinib in several SC-implanted tumor xenograft models expressing mutant variants of HER2 including an HER2 exon 20 YVMA activation insertion mutation (A775_G776insYVMA; Study ARP559, reviewed by Dr. Kufrin), HER2 exon 20 G776>VC insertion mutation (Study TKD-BCS-00191-R1), HER2

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V695E (Study TKD-BCS-00065-R1), and HER2 S310F (Study TKD-BCS-00093-R1). When the mean tumor volume was ~78–140 mm^3, mice were treated with vehicle or mobocertinib for 7-14 days. Daily oral administration of ≥50 mg/kg (A775_G776insYVMA) or ≥30 mg/kg (V695E, S310F, G776>VC) mobocertinib inhibited xenograft growth compared to vehicle control without inducing significant toxicity based on body weight loss, with the exception of 9.5% body weight loss seen at the 100 mg/kg dose level. Thus, mobocertinib also exhibited in vivo anti-tumor activity against the HER2 mutations tested. In Study ARP559, the plasma level of mobocertinib peaked at 2 or 6 hours post-dose and was substantially decreased by 24 hours post-dose. Plasma levels of metabolite AP32914 were generally 6- to 14-fold lower and levels of metabolite AP32960 were several fold higher than those of mobocertinib.

Table 6: Summary of In Vivo Anti-Tumor Activity in Mouse Xenograft Models Expressing HER2 Mutant Variants

Study #	Xenograft Model	Dose and frequency	Endpoints
ARP559	Ba/F3-HER2 exon 20 YVMA activation insertion (A775_G776insYVMA)	50 mg/kg QD 100 mg/kg QD	70% TGI (Day 7) 26% tumor regression
Study TKD-BCS-00191-R1	Ba/F3-HER2 exon 20 G776>VC insertion	30 mg/kg QD 50 mg/kg QD	49% GRI (Day 15) 73% GRI
TKD-BCS-00065-R1	Ba/F3-HER2 V695E	30 mg/kg QD 50 mg/kg QD	49% GRI (Day 14) 59% GRI
Study TKD-BCS-00093-R1	Ba/F3-HER2 S310F	30 mg/kg QD 50 mg/kg QD	60% GRI (Day 12) 83% GRI

QD = once daily; GRI = growth rate inhibition ([mean growth rate of the control group − mean growth rate of a treated group] ÷ mean growth rate of the vehicle group); TGI = Tumor growth inhibition (1-[ΔT/ΔC]) x 100, where ΔT is the mean change in tumor volume for the treatment group and ΔC is the mean change in tumor volume for the control group; (reviewer-generated table based on results from studies listed in table)

5.3.2 Secondary Pharmacodynamics

The Applicant's Position:

In a cell growth assay, mobocertinib demonstrated a relative 2-fold inhibitory activity against a *BRAF*-driven NSCLC model compared to WT EGFR-overexpressing A431 cells but no substantial inhibitory activity against *KRAS*-, *MET*-, *PGDFR*-, and *ALK*-driven NSCLC models, suggesting specificity of mobocertinib inhibitory activity toward mutant *EGFR*- and *HER2*-driven cancer cells.

The in vivo efficacy of mobocertinib was evaluated in mice bearing NCI-H1993 (*MET*-amplified) or Calu-6 (*KRAS* mutation Q61K) NSCLC xenografts; mobocertinib did not have significant anti-tumor activity in either model.

In non-tumor-bearing mice, oral administration of a single dose of mobocertinib resulted in limited inhibition of endogenous WT EGFR signaling in lung at 6 hours with a full recovery of WT EGFR signaling at 24 hours. As WT EGFR inhibition is linked to on-target toxicity, these

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results indicate that mobocertinib transiently inhibits WT EGFR in vivo, providing additional evidence that mobocertinib has potentially an acceptable on-target safety profile.

The FDA's Assessment:

FDA confirmed the Applicant's in vitro and in vivo findings. The concentration of mobocertinib required to inhibit the growth of KRAS, ALK, MET, PDGFR and BRAF mutant NSCLC cell lines in cell growth assays was 2- to 206-fold higher than the concentration required to inhibit WT EGFR activity (Study TKD-BCS-0067-R1).

5.3.3 Safety Pharmacology

The Applicant's Position:

Safety pharmacology assessments included an in vitro off-target screen, a hERG assay, and evaluations of the cardiovascular, respiratory, and central nervous systems in rat and dog toxicity studies of up to 3 months in duration at dose levels up to 1 mg/kg in dogs or 10 mg/kg in rats. The in vitro screening assessment demonstrated no off-target binding or functional effects of mobocertinib at <5 μM or of AP32914 or AP32960 at <1 μM. Mobocertinib, AP32960, and AP32914 inhibited the hERG current in a concentration-dependent manner with IC_{50} values of 10, 10, and 5.1 μM, respectively. Given that the IC_{50} values for mobocertinib, AP32960, and AP32914 were >5 μM, these compounds are not deemed to be potent hERG inhibitors. There were no mobocertinib-related effects on the cardiovascular, respiratory, or central nervous systems that indicated mobocertinib or its 2 active metabolites pose a safety pharmacology-related risk in humans.

The FDA's Assessment:

FDA generally agrees with the Applicant's conclusions.

The Applicant evaluated the off-target binding and activity of mobocertinib and its metabolites AP32914 and AP32960 (Study TKD-BCS-00402-R1). In the binding assay, incubation with 10 μM mobocertinib or metabolites led to >50% inhibition of 14 of the 86 targets (receptors, ion channels, transporters) tested. AP32914 and/or AP32960 showed >50% inhibition of an additional 11 targets that were not inhibited by mobocertinib. IC_{50} values were not provided in the study report. In the in vitro functional assay, mobocertinib and metabolites were assessed against 46 targets at concentrations of 0.0005 to 10 μM. No off-target functional effects were observed for mobocertinib at concentrations < 5 μM or for AP32914 or AP32960 at <1 μM; AP32914/AP32960 inhibited 7 targets at >1 μM. Given the micromolar concentrations in these screening assays (1–5 μM) relative to the unbound C_{max} at the 160 mg clinical dose (1.2 nM), the potential off-target activity of mobocertinib and its two metabolites appears low.

In Study 100022290 (reviewed by Dr. Kufrin), inhibition of the hERG potassium channel by mobocertinib and metabolites AP32914 and AP32960 was evaluated in vitro using the automated patch-clamp system. Mobocertinib, AP32914, and AP32960 inhibited the hERG current at concentrations >5 μM, suggesting minimal risk of QT prolongation through this pathway in humans who receive mobocertinib based on the free C_{max} at the 160 mg clinical dose.

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Additionally, the in vivo assessments included in the 1- and 3- month toxicology studies in dogs did not show QT prolongation or any other ECG effect. Although there was not a strong QT signal in nonclinical studies, QT prolongation, including resultant life-threatening arrhythmias, occurred in patients treated with mobocertinib. No stand-alone animal safety pharmacology studies were conducted with mobocertinib.

5.4 ADME/PK

The Applicant's Position:

The PK of mobocertinib following IV administration was characterized by high systemic clearance in mice and rats and a low systemic clearance in dogs, and a high volume of distribution at steady-state in all 3 species. The $t_{1/2}$ in mice, rats, and dogs was short, moderate, and very long, respectively. Oral bioavailability was moderate in mice and dogs and moderate-to-poor in rats. In rats, [^{14}C]-mobocertinib was widely distributed in tissues throughout the body with a suggestion of partially reversible association with melanin. Mobocertinib and its active metabolites were highly bound to preclinical species and human plasma proteins and binding was independent of concentration. Mobocertinib and the active metabolite AP32960 did not show preferential distribution into RBCs over plasma in preclinical species and human whole blood. Primary metabolite pathways in preclinical and human liver microsomes included N-dealkylation; no unique human metabolites were detected. The major clearance mechanism of mobocertinib was metabolism in rats and dogs with elimination primarily in the feces via biliary excretion.

The FDA's Assessment:

FDA generally agrees with the Applicant's summaries of the nonclinical ADME/PK data. All of the in vitro PK drug interaction studies (e.g., cytochrome P450 metabolism and transporter studies) were reviewed by the clinical pharmacology team as part of their assessment, so these studies were not reviewed by the nonclinical team. See Section 6 for FDA's assessment of these studies.

Type of Study	Major Findings
Absorption	
Study ARP570: Preclinical PK of mobocertinib and metabolites AP32960 and AP32914 in rats	Male Sprague-Dawley (SD) rats received mobocertinib succinate at a single intravenous (IV) dose of 3 mg/kg or oral dose of 10 mg/kg.

Mean PK Parameters of Mobocertinib and Metabolites AP32960 and AP32914 in Rats

	Mobocertinib		AP32960		AP32914	
Parameter	**IV**	**PO**	**IV**	**PO**	**IV**	**PO**
Dose (mg/kg)	3.0[a]	10.0[b]	-	-	-	-
C(0) (ng/mL)	535	-	-	-	-	-
Cmax (μg/mL)	-	29.1	-	7.63	-	9.53
T_{max} (h)	-	6.00	-	6.00	-	6.00
T_{last} (h)	24.0	24.0	7.00	24.0	7.00	8.00
AUC_{last} (h*ng/mL)	927	397	58.9	101	66.9	121
AUC_{24} (h*ng/mL)	934	444	64.2	113	66.4	ND
CL (mL/min/kg)	54.5	-	-	-	-	-
V_{ss} (L/kg)	11.5	-	-	-	-	-
$t_{1/2}$ (h)	3.58	3.16	7.49	4.08	5.55	ND
Oral bioavailability (%)	-	14.3	-	-	-	-

ND: not determined; AUC_{24}: area under the concentration-time curve from 0 to 24 hours; AUC_{last}: area under the concentration-time curve from 0 to time of last quantifiable concentration; C(0): concentration at time zero extrapolated by linear regression from the apparent distribution phase following IV administration; CL: clearance; C_{max}: maximum observed plasma concentration; IV: intravenous; PO: oral; $t_{1/2}$: half-life; T_{last}: time of last observed quantifiable concentration; T_{max}: time of first occurrence of C_{max}; V_{SS}: volume of distribution at steady state
[a]Solution in HPLC water
[b]Suspension in 1% Pluronic F68/0.5% carboxymethylcellulose (90:10, v:v)

Study ARP572: Preclinical PK of mobocertinib and metabolites AP32960 and AP32914 in dogs	Male Beagle dogs received mobocertinib succinate at a single IV dose of 3 mg/kg or oral dose of 25 mg/kg.

Type of Study	Major Findings

Mean PK Parameters of Mobocertinib and Metabolites AP32960 and AP32914 in Dogs									
	Mobocertinib			AP32960			AP32914		
Parameter	**IV**	**PO Susp**	**PO Cap**	**IV**	**PO Susp**	**PO Cap**	**IV**	**PO Susp**	**PO Cap**
Dose (mg/kg)	3.0[a]	25.0[b]	25.0[c]	-	-	-	-	-	-
C(0) (ng/mL)	517	-		-	-	-	-	-	-
C_{max} (µg/mL)	-	565	536	-	89.7	66.7	-	37.7	32.4
T_{max} (h)	-	6.00	6.00	-	8.00	4.00	-	8.00	9.33
T_{last} (h)	72.0	72.0	72.0	64.0	72.0	72.0	48.0	72.0	72.0
AUC_{last} (h*ng/mL)	4638	13,535	13,987	279	1941	1850	188	991	1098
AUC_{72} (h*ng/mL)	4638	13,535	13,987	286	1941	1850	204	991	1098
AUC_{24} (h*ng/mL)	3162	9038	9168	179	1374	1181	124	578	582
CL (mL/min/kg)	11.2	-	-	-	-	-	-	-	-
V_{ss} (L/kg)	12.4	-	-	-	-	-	-	-	-
$t_{1/2}$ (h)	13.9	14.9	16.0	15.6	11.7	13.2	14.1	15.5	16.4
Oral bioavailability (%)	-	37.6	38.9	-	-	-	-	-	-

Susp: suspension; Cap: capsule ND: not determined; AUC_{24}: area under the concentration-time curve from 0 to 24 hours; AUC72: area under the concentration-time curve from 0 to 72 hours; AUC_{last}: area under the concentration-time curve from 0 to time of last quantifiable concentration; C(0): concentration at time zero extrapolated by linear regression from the apparent distribution phase following IV administration; CL: clearance; C_{max}: maximum observed plasma concentration; IV: intravenous; PO: oral; $t_{1/2}$: half-life; T_{last}: time of last observed quantifiable concentration; T_{max}: time of first occurrence of C_{max}; V_{SS}: volume of distribution at steady state
[a]Solution in PEG400/ethanol (80:20, v:V)
[b]Suspension in 1% Pluronic F68/0.5% carboxymethylcellulose (10:90, v:v)
[c]Drug (mobocertinib succinate) in capsule

Distribution

Study NCDS-02651_Report-313N-1733 Amendment 1: Blood, plasma, and tissue distribution in male rats after oral administration of [^{14}C] mobocertinib	Following single oral administration of 10 mg/kg [^{14}C]mobocertinib to male Long-Evans (LE) and SD rats, the tissue distribution of total radioactivity was determined by whole-body autoradiography for up to 2160 hours after dosing. Blood-to-plasma radioactivity concentration ratios in the LE rats ranged from 0.78–0.84 in the first 8 hours post-dose and increased to 1.16–1.94 at 48–96 hours post-dose. [^{14}C]mobocertinib-derived radioactivity was widely distributed throughout the body of LE rats (33/44 tissues) through 168 hours post-dose. The highest mean C_{max} values were observed in the liver, adrenal gland cortex, adrenal gland, kidney outer medulla, alimentary canal, eye uvea, thyroid, bile, and urine. Tissues with the lowest mean C_{max} values were seminal vesicles, testis, bone, spinal cord, brain tissues (0.064 µg equiv/g), and eye lens. C_{max} was observed in 25/44 tissues at 4 hours post-dose, with higher concentrations in most tissues than in blood. The elimination of radioactivity was slow, with $t_{1/2}$ >100 hours for many tissues. The eye (uvea) of LE rats had the overall highest exposure (AUC) to [^{14}C]mobocertinib, which showed a partially reversible association with melanin. The tissue distribution of [^{14}C]mobocertinib-derived radioactivity in male SD rats was similar to that of LE rats, but C_{max} in the tissue of SD rats was approximately 1.6-fold higher than that in LE rats.

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<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Study ARP568:
In vitro binding of mobocertinib and metabolites AP32960 and AP32914 to mouse, rat, dog, and human plasma proteins</td><td>Mobocertinib and metabolites AP32960 and AP32914 were highly bound to mouse, rat, dog, and human plasma proteins, with no significant difference in protein binding between any species tested. Plasma protein binding was generally concentration-independent in all species tested.
<table>
<tr><th></th><th colspan="3">Overall Mean % Binding in Plasma</th></tr>
<tr><th>Species</th><th>Mobocertinib</th><th>AP32960</th><th>AP32014</th></tr>
<tr><td>Mouse</td><td>99.5</td><td>99.4</td><td>98.9</td></tr>
<tr><td>Rat</td><td>99.5</td><td>99.5</td><td>98.2</td></tr>
<tr><td>Dog</td><td>99.3</td><td>99.6</td><td>98.0</td></tr>
<tr><td>Human</td><td>99.3</td><td>99.5</td><td>98.6</td></tr>
</table></td></tr>
<tr><td>Study ARP569:
In vitro assessment of blood-to-plasma partitioning of mobocertinib and metabolite AP32960 in mouse, rat, dog, and human whole blood</td><td>Following in vitro incubation of mouse, rat, dog, and human whole blood with 0.1, 0.5, 1, and 5 μM mobocertinib or metabolite AP32960, mobocertinib and AP32960 preferentially distributed in the plasma over red blood cells in all species tested. Mobocertinib and AP32960 partitioning was concentration-independent.
<table>
<tr><th></th><th colspan="2">Blood to Plasma Partitioning Ratio</th></tr>
<tr><th>Species</th><th>Mobocertinib</th><th>AP32960</th></tr>
<tr><td>Mouse</td><td>0.98</td><td>1.17</td></tr>
<tr><td>Rat</td><td>1.14</td><td>1.23</td></tr>
<tr><td>Dog</td><td>1.42</td><td>12.5</td></tr>
<tr><td>Human</td><td>0.95</td><td>1.01</td></tr>
</table></td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td>Study NCDS-02615:
Intrinsic clearance of mobocertinib and metabolites AP32960 and AP32914 in mouse, rat, dog, and human liver microsomes and hepatocytes</td><td>Mobocertinib exhibited moderate to high clearance, and metabolites AP32960 and AP32914 showed low to moderate clearance in mouse, rat, dog, and human liver microsomes.
Mobocertinib and AP32960 showed moderate clearance in all four species of hepatocytes tested. AP32914 showed moderate clearance in rat, dog, and human hepatocytes and low clearance in mouse hepatocytes.</td></tr>
</table>

Reference ID: 4857343

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Study ARP588:
In vitro metabolism of mobocertinib in mouse, rat, dog, and human liver microsomes and hepatocytes</td><td>Mobocertinib showed moderate-to-high clearance in all species tested, with a metabolic rate in liver microsomes of mouse > human/rat > dog; and in hepatocytes of rat > human > dog.

<table>
<tr><th colspan="7">% Radioactivity in Microsomal Incubates with NADPH (30 min Incubation)[a]</th></tr>
<tr><th>Met ID</th><th>Observed [MH]+</th><th>RT (min)</th><th>MsLM</th><th>RLM</th><th>DLM</th><th>HLM</th></tr>
<tr><td>M55</td><td>602.3072</td><td>53.8</td><td>1.42</td><td>1.8</td><td>4.84</td><td>-</td></tr>
<tr><td>M59</td><td>515.2390</td><td>55.7</td><td>1.84</td><td>5.44</td><td>-</td><td>-</td></tr>
<tr><td>M61</td><td>572.2971</td><td>58.7</td><td>2.14</td><td>6.09</td><td>1.69</td><td>2.49</td></tr>
<tr><td>M62/M63</td><td>588.2912/602.3072</td><td>59.4</td><td>0.70</td><td>0.94</td><td>0.95</td><td>2.11</td></tr>
<tr><td>M67 (AP32960)</td><td>572.2954</td><td>63.2</td><td>29.71</td><td>5.59</td><td>12.31</td><td>15.9</td></tr>
<tr><td>M68</td><td>602.3072</td><td>63.8</td><td>1.37</td><td>1.37</td><td>2.94</td><td>1.84</td></tr>
<tr><td>AP32788 (parent)</td><td>586.3133</td><td>66.3</td><td>54.16</td><td>65.73</td><td>67.57</td><td>63.58</td></tr>
</table>

[a]Only peaks containing >1% of the total radioactivity in each matrix are listed
RT = Retention time; Ms = Mouse; R = Rat; D = Dog; H – Human; LM = Liver microsomes

<table>
<tr><th colspan="7">Percentage of [^{14}C]AP32788 and its Metabolites in Incubations with Human, Dog, Rat, and Mouse Hepatocytes</th></tr>
<tr><th rowspan="2">Met ID</th><th rowspan="2">Observed [MH]+</th><th rowspan="2">RT (min)</th><th colspan="4">% Radioactivity in Hepatocyte Incubates (60 min Incubation)[a]</th></tr>
<tr><th>Human</th><th>Dog</th><th>Rat</th><th>Mouse</th></tr>
<tr><td>M8</td><td>822.3241</td><td>26.0</td><td>-</td><td>-</td><td>3.87</td><td>-</td></tr>
<tr><td>M23</td><td>879.3812</td><td>31.2</td><td>-</td><td>-</td><td>-</td><td>2.89</td></tr>
<tr><td>M31</td><td>893.3984</td><td>35.0</td><td>-</td><td>-</td><td>2.76</td><td>-</td></tr>
<tr><td>M52</td><td>501.2251</td><td>47.6</td><td>-</td><td>2.59</td><td>1.16</td><td>-</td></tr>
<tr><td>M57</td><td>618.3029</td><td>49.6</td><td>-</td><td>-</td><td>2.27</td><td>-</td></tr>
<tr><td>M59</td><td>515.2390</td><td>50.0</td><td>-</td><td>-</td><td>1.74</td><td>-</td></tr>
<tr><td>M61</td><td>572.2971</td><td>52.3</td><td>-</td><td>2.45</td><td>8.39</td><td>1.33</td></tr>
<tr><td>M63</td><td>602.3072</td><td>53.1</td><td>-</td><td>-</td><td>-</td><td>2.29</td></tr>
<tr><td>M67 (AP32960)</td><td>572.2954</td><td>59.1</td><td>12.7</td><td>12.6</td><td>8.37</td><td>33.5</td></tr>
<tr><td>M68</td><td>602.3072</td><td>59.8</td><td>-</td><td>-</td><td>-</td><td>9.23</td></tr>
<tr><td>AP32788 (parent)</td><td>586.3132</td><td>63.7</td><td>45.3</td><td>61.32</td><td>27.9</td><td>10.9</td></tr>
</table>

[a]Only peaks containing >1% of the total radioactivity in each matrix are listed; RT = Retention time; - = Not detected

The microsomal and hepatocyte metabolites of mobocertinib were mainly due to N-dealkylation (M52, M59, M61, M67 [AP32960]) and oxidation (M55, M57, M63, M68), and no unique human metabolites were detected. In human hepatocytes, the only metabolite observed was AP32960, which was also the major metabolite in the nonclinical species tested. Mobocertinib was primarily metabolized by CYP3A4/5.</td></tr>
<tr><td>Study ARP597:
Metabolite profiling of mouse and dog plasma after oral administration of mobocertinib</td><td>The Applicant compared the metabolic profiles of mobocertinib in plasma collected from beagle dogs, CD-1 mice (both species, Study ARP597), and rats (Study ARP589). The metabolite profiles were similar among the three species. The majority of metabolites identified were due to N-dealkylation, oxidation, and oxidation plus N-dealkylation. M67 (AP32960) and M65 (AP32914) were detected in dog, mouse, and rat plasma.</td></tr>
</table>

Type of Study	Major Findings
Study NCDS-02618: In vitro binding of mobocertinib and metabolites AP32960 and AP32914 to human liver microsomal proteins	The binding of mobocertinib and metabolites AP32960 and AP32914 to human liver microsomal proteins was high, at 99.6%, 99.6%, and 98.5%, respectively. The recovery of all three was ≥91.2%, and the percentage remaining (stability in matrix) was ≥101.1%.
Excretion	
Study ARP589: Excretion, PK, and metabolic profiling in plasma, urine, bile, and feces of male rats following oral administration of [^{14}C] mobocertinib	Following single oral (20 mg/kg) administration of [^{14}C]mobocertinib to male SD rats, the major route of elimination was through fecal excretion (~97%) and urinary excretion was minor (~2%). The majority (89%) of the dose was excreted by 24 hours. <u>Metabolic profiling results</u> **Plasma:** Mobocertinib was the major circulating component in rat plasma, contributing 20.48% of the total radioactivity (TRA). The plasma metabolites were largely N-dealkylated and oxidative metabolites. Metabolites M65 (AP32914) and M67 (AP32960) contributed 1.22% and 6.58% of plasma TRA, respectively. **Urine:** The urine metabolite profile comprised 20 metabolites, which were largely N-dealkylated and oxidative metabolites, and GSH conjugates of the Phase I metabolites. Metabolites M65 and M67 contributed 0.01% and 0.1% of urine TRA, respectively. **Bile:** The bile metabolite profile comprised 30 metabolites, which were largely GSH adducts and further products of the glutathione biotransformation pathway. Metabolites M65 and M67 contributed 0.03% and 0.93% of bile TRA, respectively. **Feces:** The fecal metabolite profile comprised ~35 metabolites, which were largely due to GSH conjugation and products of further biotransformation of the GSH adducts. Metabolites M65 and M67 contributed 0.01% and 0.27% of feces TRA, respectively.

Type of Study	Major Findings
Study TKD-BCS-00238-R1 Amendment 1: Metabolic profiling in plasma, urine, bile, and feces of male dogs following oral administration of [^{14}C] mobocertinib	Following single oral (10 mg/kg) administration of [^{14}C]mobocertinib to male Beagle dogs mobocertinib underwent extensive biotransformation. The major route of elimination was through fecal excretion (~46%). Three metabolites, M106, M107, and M108 (also known as M59), identified in human plasma were also detected in dog plasma, urine, feces, and bile at very low levels. <u>Metabolic profiling results</u> **Plasma:** Unchanged mobocertinib was the major circulating component in plasma, contributing 68.5% of the TRA. Circulating metabolites M53, M66, *M67 (AP32960)*, and M98 represented 3.9%, 5.1%, 15.0%, and 7.5% of TRA, respectively. **Urine (7% dose recovery):** Unchanged mobocertinib and M70 accounted for 22.6% and 25.8% of TRA, respectively. Additional compounds representing <8.4% of TRA included M53, M60, M66, *M67*, M78, M79, M82, M83, M89, M90 and M98. **Bile (40.3% dose recovery):** M53 and *M67* were the major metabolites, accounting for 14.8% and 14.0% of TRA, respectively. Additional compounds representing <10% of TRA included M60, *M65 (AP32914)*, M66, M70, M80 to M104 and mobocertinib. **Feces (45.9% dose recovery):** M70 was the most abundant drug-related metabolite, accounting for 32.9% of TRA. Additional compounds representing <9.5% of TRA included M53, M60, *M65*, M66, *M67*, M82, M83, M85, M87, M90, M97, M98, M99, M105 and mobocertinib. *Active human metabolites AP32960 and AP32914 are italicized AP32914 and AP32960 are pharmacologically active circulating human metabolites. There were no human-specific metabolites, as AP32914 and AP32960 were also rat, mouse, and dog metabolites. Plasma levels of these metabolites were reasonably similar between animals and humans in the toxicology studies. There was adequate safety coverage, and no additional toxicological assessment of metabolites is warranted.

5.5 Toxicology

5.5.1 General Toxicology

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

The single-dose and repeat-dose toxicology studies evaluated the toxicity of mobocertinib, the reversibility of effects, and exposures of mobocertinib and its 2 active metabolites, AP32960 and AP32914, both of which were found in similar proportions between animals and humans. In rat and dog toxicity studies, daily administration of mobocertinib resulted in exposures of mobocertinib, AP32960, and AP32914 that increased in a manner either approximately proportional to dose or greater than proportional to dose. In the 3-month studies, exposures generally increased after repeated administration. Female rats had higher exposures than males, which was likely due to differences in metabolism, while in dogs there were no sex-based differences in exposures. Clinical signs associated with dose-limiting toxicity were similar between rats and dogs and were often related to effects on the gastrointestinal system, including fecal changes, emesis, decreased food consumption, and body weight loss. At non-tolerated doses the body weight losses led to dosing holidays in both species. Additionally, at the highest doses evaluated in rats there was evidence of overt toxicity that affected multiple organ systems. Dogs were generally more sensitive to mobocertinib than rats based on a comparison of both

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body surface area-adjusted doses and by exposures. The main toxicities associated with mobocertinib administration were similar between rats and dogs, and included changes in the gastrointestinal tract (atrophy, single cell necrosis, mononuclear cell infiltration), reproductive system (atrophy and single cell necrosis), hematological system (acute phase responses), and the squamous epithelium (decreased thickness) in multiple organs, such as the skin and oral cavity. These findings were generally related to dose and/or exposure, were consistent with EGFR inhibition, and have generally been seen with other EGFR inhibitors. These effects were fully or partially reversible with a recovery period.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment of the toxicology data. In addition to the clinical signs highlighted by the Applicant, skin abnormalities were also seen in rats and dogs including red, dry, flaking skin and histopathological findings of atrophy, hyperplasia, and inflammation. In dogs, mobocertinib was not tolerated in males at the high dose of 1 mg/kg, as evidenced by clinical toxicities in the oral cavity (ulceration) leading to early euthanasia. Ocular effects of eye discharge, corneal opacity, and/or conjunctival hyperemia correlating microscopically with atrophy of the corneal epithelium also occurred in dogs.

Study title/number: A 3-Month Oral Study of TAK-788 by Oral Gavage in Sprague-Dawley Rats with a 1-Month Recovery Period/8002352 Amendment 1

Key Study Findings

- There were no mobocertinib-related mortalities.
- The main clinical observations were skin abnormalities at all doses.
- High dose rats had decreased mean body weight and mean body weight gain.
- Target organs included the GI tract, reproductive tract, skin, mandibular lymph node, kidney, and sublingual salivary gland.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	Males: 0, 2.5, 5, and 10 mg/kg Females: 0, 1.25, 2.5, and 5 mg/kg (lower doses were administered to females because the exposure and maximal plasma concentration were ~2-fold higher for females than males in the 28-day toxicology study) Once daily for up to 3 months
Route of administration:	Oral gavage
Formulation/Vehicle:	25 mM citrate buffer, pH 2.75
Species/Strain:	Rat/Sprague-Dawley Crl:CD(SD)
Number/Sex/Group:	Main: 10 rats/sex/group

	Recovery: 5 rats/sex/group
Age:	8 weeks old
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No mobocertinib-related deaths • Four rats (including 2 controls) were found dead or euthanized prematurely for procedural reasons (gavage, bleeding) or traumatic causes (fracture, cage accident).
Clinical Signs	The main findings were skin abnormalities, which persisted throughout the recovery period. <u>Males</u> **2.5 mg/kg:** red skin **5 mg/kg:** red skin, dry skin, soft feces **10 mg/kg:** red skin, dry skin and fur, hypersensitivity (increased incidence compared to controls), thin fur, scab on tail, soft feces, thinness and prominent backbone, flaking skin <u>Females</u> **1.25 mg/kg:** red skin, dry skin, flaking skin **2.5 mg/kg:** red skin, dry skin, hypersensitivity (1 female) **5 mg/kg:** red skin, dry skin and dry fur, thin fur, scab on muzzle, flaking skin
Body Weight	**10 mg/kg males:** ≤11% decrease in mean body weight and 17% decrease in mean body weight gain, which showed evidence of recovery **5 mg/kg females:** ≤9% decrease in mean body weight and 18% decrease in mean body weight gain; which was not reversible
Feed Consumption	**≥5 mg/kg males:** 9% decrease in food consumption, which showed evidence of recovery **≥2.5 mg/kg females:** 12% decrease in food consumption, which showed evidence of partial recovery
Ophthalmoscopy	No findings
Hematology	Findings included decreased reticulocytes (females only); and increased WBCs, neutrophils, monocytes, and platelets (males only), consistent with inflammation. Increased WBCs in males at 10 mg/kg and decreased reticulocytes in females were still observed during the recovery period.

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Hematology: % Change from Concurrent Control (3-Month Study; Rats)

		Males			Females		
	Day	2.5 mg/kg	5 mg/kg	10 mg/kg	1.25 mg/kg	2.5 mg/kg	5 mg/kg
Leukocytes	92	-11%	11%	**31%**	24%	9%	**48%**
	120	21%	-2%	41%	-0.1%	23%	5%
Monocytes	92	-23%	-7%	**51%**	26%	-15%	**66%**
	120	2%	-28%	9%	-18%	-14%	-4%
Neutrophils	92	-25%	27%	***193%***	0.3%	-3%	***114%***
	120	-6%	-12%	39%	-30%	-28%	-27%
Platelets	92	0.4%	**14%**	**15%**	-0.1%	3%	3%
	120	-4%	-3%	1%	3%	0.3%	13%
Reticulocytes	92	13%	19%	9%	-16%	**-18%**	**-16%**
	120	-30%	-23%	-23%	-23%	-31%	-32%

% relative to controls during on Days 92 (day of necropsy) and 120 (Recovery group); Green denotes %↑; Bold: P ≤ 0.05; Bold and italic: P ≤ 0.01

Coagulation	20% and 15% reversible increases in fibrinogen in 10 mg/kg males and 5 mg/kg females, respectively
Clinical Chemistry	Findings included decreases in albumin, albumin to globulin ratio, creatine kinase, and triglycerides (males only); and increases in liver enzymes (ALT, AST – associated with spontaneous foci of liver necrosis in 2 males and 3 females), urea nitrogen, and globulin. Changes were generally fully or partially reversible.

Clinical Chemistry: % Change from Concurrent Control (3-Month Study; Rats)

		Males			Females		
Test	Day	2.5 mg/kg	5 mg/kg	10 mg/kg	1.25 mg/kg	2.5 mg/kg	5 mg/kg
ALT	92	7%	32%	***77%****	29%	20%	**60%**
	120	-16%	-23%	-3%	-2%	6%	12%
Albumin	92	2%	-3%	***-8%***	-2%	-8%	-8%
	120	-4%	-3%	-6%	5%	5%	4%
Albumin/Globulin	92	-4%	-11%	***-22%****	2%	-14%	**-16%**
	120	-11%	-13%	-7%	3%	-1%	-7%
AST	92	20%	26%	57%	33%	22%	49%
	120	-5%	16%	19%	-14%	-7%	34%
Creatine Kinase	92	5%	-14%	-20%	9%	-60%	-58%
	120	-34%	18%	5%	-42%	-30%	-26%
Globulin	92	6%	8%	***17%****	-1%	7%	11%
	120	7%	11%	1%	2%	8%	12%
Triglycerides	92	-4%	**-36%**	***-39%***	7%	-7%	-2%
	120	15%	-7%	15%	-14%	-47.34%	-33%
Urea Nitrogen	92	4%	***22%***	***26%****	5%	16.95%	**31%**
	120	-2%	-11%	-8%	9%	8.77%	26%

% relative to controls during on Days 92 (day of necropsy) and 120 (Recovery group); Green denotes %↑; Bold: P ≤ 0.05; Bold and italic: P ≤ 0.01; Bold, italic: *P ≤ 0.001

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Urinalysis	**Males:** Increases in specific gravity (99–129%) on Day 29 in all dose groups and Week 13 (51%) in the 10 mg/kg group; and decreases in urine volume (60–72%) on Day 29 in all dose groups and Week 13 (52%) in the 10 mg/kg group relative to the control group **Females:** No findings
Gross Pathology	Mandibular lymph node enlargement in 5 and 10 mg/kg males and 1.25 and 5 mg/kg females correlated histologically with lymphoid hyperplasia. Thin hair coat on 10 mg/kg males correlated histologically with inflammation of hair follicles and hair bulb atrophy in the skin.
Organ Weights	Findings included decreased prostate (≥5 mg/kg) and uterus (≥1.25 mg/kg) weights up to ~40% compared to controls, which correlated histologically with epithelial atrophy.
Histopathology **(Adequate battery: Yes)**	Refer to Table 7 for selected histopathology findings. The main target organs included the GI tract, reproductive tract, skin, eyes, larynx, mandibular lymph node, kidney, and sublingual salivary gland.
Other Evaluations	No test article-related neurological abnormalities
Toxicokinetics	• Exposure to mobocertinib increased in a generally dose-proportional manner on Days 1 and 91. • Exposure to the AP32914 and AP32960 metabolites generally increased in a greater than dose proportional manner on Day 1 and nearly dose proportional manner on Day 91. • Mobocertinib exposures were ≤2-fold higher in females compared to males. • There was accumulation of mobocertinib and its metabolites, as noted by the following accumulation ratios (ARs) based on the AUC(0-t): - Mobocertinib: 2.34–2.90 in males; 2.50–3.32 in females - AP32914: 1.31–3.96 in males; 1.52–5.86 in females - AP32960: 2.44–8.03 in males; 13.7–14.7 in females

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Toxicokinetic Parameters for Mobocertinib

	Males			Females		
mg/kg	**2.5**	**5**	**10**	**1.25**	**2.5**	**5**
Day 1						
Tmax (h)	4	4	4	4	4	4
Cmax (ng/mL)	10.7	28.4	62.7	5.80	21.6	41.5
AUC(0-t) (ng·h/mL)	114	278	629	78.2	232	494
Day 91						
Tmax (h)	4	4	4	2	4	4
Cmax (ng/mL)	24.1	66.5	101	19.9	42.3	91.3
AUC(0-t) (ng·h/mL)	303	806	1470	259	581	1310

h = hours; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

Toxicokinetic Parameters for Metabolite AP32914

	Males			Females		
mg/kg	**2.5**	**5**	**10**	**1.25**	**2.5**	**5**
Day 1						
Tmax (h)	4	4	4	4	4	4
Cmax (ng/mL)	1.49	4.04	8.08	0.76	2.46	4.96
AUC(0-t) (ng·h/mL)	7.5	19.6	105	4.10	14.0	66.7
Day 91						
Tmax (h)	4	4	8	2	4	4
Cmax (ng/mL)	2.18	5.27	9.33	2.05	3.99	6.44
AUC(0-t) (ng·h/mL)	29.8	73.5	137	23.7	52.9	101

h = hours; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

Toxicokinetic Parameters for Metabolite AP32960

	Males			Females		
mg/kg	**2.5**	**5**	**10**	**1.25**	**2.5**	**5**
Day 1						
Tmax (h)	4	4	4	8	4	4
Cmax (ng/mL)	1.52	3.53	10.9	0.08	0.72	1.50
AUC(0-t) (ng·h/mL)	8.8	47.8	134	NR1	4.2	9.7
Day 91						
Tmax (h)	4	4	4	4	2	4
Cmax (ng/mL)	4.85	12.4	25.6	1.85	3.89	11.3
AUC(0-t) (ng·h/mL)	70.2	163	327	20.4	57.7	142

h = hours; NR1 = Not reportable due to < 3 measurable concentrations at separate time points; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

Table 7: Selected Histopathology Findings (3-Month Study; Rats)

			Male				Female			
Organ/Tissue	Finding	Dose (mg/kg)	0	2.5	5	10	0	1.25	2.5	5
# of Rats Examined (dosing/recovery)			9/4R	9/5R	9/5R	10/5R	10/5R	10/5R	10/5R	10/5R
Lymph Node, Mandibular	Increased cellularity; lymphoid	Minimal	3/2R	5/2R	4/1R	7	1/2R	4/2R	4/2R	4/2R
		Mild	3	3/1R	4/2R	2/4R	3/2R	1/2R	2R	4/3R
		Moderate	1/1R	1R	1/1R	1R		1	1R	
	Plasmacytosis	Minimal	3	1	3	6	1	2	1	4
		Mild			1	2				1
Skin	Atrophy; hair bulb	Minimal				2/2R				2
		Mild			1/1R	1/1R				1
		Moderate				4				3
	Hyperplasia; epidermal, multifocal	Minimal				2				
		Mild				2				
	Inflammation, mixed cell; focal, multifocal, follicle	Minimal			4/1R	1/4R				5
		Mild				4				
		Moderate				5				2
Vagina	Decreased thickness; epithelial	Minimal						4	5	4
		Mild							3	2
		Moderate								1
	Infiltration, neutrophilic	Minimal						5	5	6
		Mild							2	1
	Mucification	Mild						1		4
Gland, Prostate	Atrophy; epithelial	Minimal		1	5	1				
		Mild			1	8				
		Moderate				1				
	Inflammation, neutrophilic; acinar, focal, multifocal	Minimal		2	4/3R	4/1R				
Large Intestine, Cecum	Atrophy; mucosa	Minimal		4	5	3/1R			2	2
		Mild			1	4				3
	Infiltration, mononuclear cell; mucosal	Minimal		7	4/1R	6		3	8	8
		Mild			2	3/1R			1	1
Kidney	Chronic progressive nephropathy; bilateral, focal, multifocal, unilateral	Minimal	1/1R	4/2R	6/2R	7/3R	1/1R	1/1R	3/2R	2/3R
		Mild			1/1R	1		1		
Large Intestine, Colon	Atrophy; mucosa	Minimal			5	3/3R			3	8
		Mild				3				
	Infiltration, mononuclear cell; mucosal	Minimal			6	8/4R			7	6/1R
		Mild			1					
Larynx[a]	Decreased thickness; epithelial, pharynx	Minimal		3	8	6/2R		2	7/1R	8/2R
		Mild				4				1
Cervix	Decreased thickness; epithelial	Minimal						1	1	
		Moderate						6	6	6
		Marked							1	4
Gland, Mammary[b]	Atrophy; lobuloalveolar	Minimal			3R	4R				
		Mild		3/1R	1R					
		Moderate		7	6	2				
		Marked			3	6				
		Severe				1				
Small Intestine, Ileum	Atrophy; villous	Minimal			5	6		3	3	5
		Mild				1		1	3	5

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			Male				Female			
Organ/Tissue	Finding	Dose (mg/kg)	0	2.5	5	10	0	1.25	2.5	5
# of Rats Examined (dosing/recovery)			9/4R	9/5R	9/5R	10/5R	10/5R	10/5R	10/5R	10/5R
Stomach	Decreased thickness; epithelial, non-glandular	Minimal		3	4	7		3	7	5
		Mild			1	2			3	3
Tongue	Decreased thickness; epithelial	Minimal		5	7	5		3	4	4
		Mild			2	5				6
Uterus	Atrophy; epithelial	Minimal						1	2	1
		Mild						3	3	
		Moderate						2	4	9
Liver	Necrosis; focal, multifocal	Minimal	1	2		2				3
		Mild						1		
Esophagus	Decreased thickness; epithelial	Minimal		1	7/1R	7/2R		1	4	8
		Moderate				1				
Eye	Decreased thickness; epithelial, cornea	Minimal			3	7				2
Gland, Salivary, Sublingual[c]	Atrophy; acinar	Minimal		2	3	5		1	2	3
		Mild				2				2
Large Intestine, Rectum	Inflammation, mixed cell; focal, follicle, adnexa, multifocal	Minimal		2/1R	1/1R	3				3
		Mild			3/1R	4/1R				
Small Intestine, Jejunum	Atrophy; villous	Minimal			1	6			1	2
		Mild								1
Small Intestine, Duodenum	Atrophy; villous	Minimal		1				1		3
		Mild			1					1

[a]Eight 5 mg/kg males and nine 2.5 mg/kg females examined; [b]eight 0 mg/kg and nine 5 mg/kg males examined; [c]seven 2.5 mg/kg males, eight 5 mg/kg males, and nine 5 mg/kg females examined

Study title/number: A 3-Month Oral Toxicity Study of TAK-788 in Beagle Dogs with a 1-Month Recovery Period/8002353

Key Study Findings

- Mobocertinib was not tolerated in males at 1 mg/kg as evidenced by adverse clinical toxicities (oral ulceration) leading to early euthanasia. Dosing was suspended for 7 days for 1 male at 0.5 mg/kg in part due to body weight loss.
- Males in the 1 mg/kg group had decreased mean body weight/body weight loss.
- Clinical observations included red and/or dry skin, ocular changes (red eyeball/discharge), soft/liquid feces, and emesis.
- Ocular effects (corneal opacity, conjunctival hyperemia) occurred at all doses.
- Target organs included the oral cavity, hard palate, lymph nodes, tongue, esophagus, female reproductive tract, skin, eye, larynx, and kidneys (males only).

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.25, 0.5, and 1 mg/kg Once daily for up to 3 months
Route of administration:	Oral gavage
Formulation/Vehicle:	25 mM citrate buffer, pH 2.75
Species/Strain:	Dog/Beagle
Number/Sex/Group:	Main: 4 rats/sex/group Recovery: 2 rats/sex/group
Age:	11 to 12 months old
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	Early mortality occurred in males in the 1 mg/kg group: • 1 male was euthanized on Day 70 in moribund condition due to a spontaneous botryoid rhabdomyosarcoma in the urinary bladder, which was not considered drug-related because symptoms of bladder cancer were present in this dog pre-treatment. • The remaining 5 dogs (main and recovery groups) were euthanized on Day 82 due to toxicities in the oral cavity (ulcers on the lips and hard palate, correlated with swelling in the palate region). Due to deteriorating health, one male at 0.5 mg/kg received a dosing holiday between Days 64 and 70.
Clinical Signs	There was a dose-dependent increase in the incidence and/or duration of the following findings in dogs at all mobocertinib dose levels compared to controls, with partial recovery: • GI distress (soft/liquid feces) • Slight swelling of the vulva region • Red and/or dry skin • Ocular effects including red eyeball and/or eye discharge • Sporadic occurrences of emesis
Body Weight	Males ≤11% decrease in mean body weight/body weight loss in 1 mg/kg males compared with controls.
Feed Consumption	Due to decreased food consumption, all animals received food supplementation with their standard feed by Day 18 (males)/17 (females), after which food consumption was generally comparable to controls, with some fluctuations that persisted into the recovery period for males.

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Ophthalmoscopy	Males **0.25 mg/kg:** No findings **0.5 and 1 mg/kg:** Conjunctival hyperemia, corneal opacity, lens opacity Females **0.25 mg/kg:** Vitreous hyaloid remnant, lens opacity, conjunctival hyperemia, serous discharge **0.5 mg/kg:** Conjunctival hyperemia, corneal opacity, lens opacity **1 mg/kg:** Conjunctival hyperemia, corneal opacity, serous discharge Findings showed evidence of partial recovery.
ECG	No findings
Hematology	Findings included minimal to mild increases in WBCs, neutrophils, monocytes, and platelets. Changes in monocytes in 0.25 and 0.5 mg/kg males did not show evidence of recovery.

Hematology: % Change from Concurrent Control (3-Month Study; Dogs)

		Male			Female		
Test	Day	0.25 mg/kg	0.5 mg/kg	1 mg/kg	0.25 mg/kg	0.5 mg/kg	1 mg/kg
Leukocytes	82/85	4%	-3%	12%	0.7%	-5%	7%
	113	2%	-3%		14%	18%	25%
Monocytes	82/85	**37%**	**37%**	78%	-0.8%	22%	**71%**
	113	42%	51%		38%	33%	9%
Neutrophils	82/85	5%	4%	17%	0.6%	-11%	6%
	113	11%	-4%		5%	26%	40%
Platelets	82/85	-3%	-0.8%	24%	2%	-4%	14.%
	113	-21%	-20%		-7%	-16%	-0.1%

% relative to controls during on Days 82[a]/85 and 113 (Recovery group); Green denotes %↑;
Bold: P ≤ 0.05; [a]5/6 surviving males at 1 mg/kg were euthanized early on Day 82, including the recovery animals

Coagulation	44% and 64% reversible increases in fibrinogen in 1 mg/kg females compared to controls during Weeks 4 and 13, respectively.
Clinical Chemistry	Findings included decreases in albumin, albumin/globulin ratio, calcium, and cholesterol; and increases in chloride and amylase. Changes were partially or fully reversible during the recovery period, with the exception of cholesterol in 1 mg/kg females.

Clinical Chemistry: % Change from Concurrent Control (3-Month Study; Dogs)

		Males			Females		
Test	Day	0.25 mg/kg	0.5 mg/kg	1 mg/kg	0.25 mg/kg	0.5 mg/kg	1 mg/kg
Albumin	82/85	-10%	***-14%****	-31%	-9%	**-10%**	***-25%****
	113	1%	0%		-1%	1%	-1%
Albumin/ Globulin	82/85	-10%	-18%	-37%	-6%	-3%	***-32%****
	113	-6%	-6%		-3%	9%	-6%
Amylase	82/85	-10%	-0.3%	23%	10%	12%	***36%***
	113	-16%	4%		-3%	5%	2%
Calcium	82/85	-10%	**-5%**	-11%	-2%	-3%	***-7%***
	113	2%	2%		6%	4%	3%
Chloride	82/85	-10%	1%	0.4%	**2%**	**2%**	***3%***
	113	0%	-0.4%		2%	0.9%	2%
Cholesterol	82/85	-10%	***-25%***	-31%	-18%	-18%	-31%
	113	15%	-3%		8%	-11%	-27%
Triglycerides	82/85	-10%	13%	8%	14%	31%	18%
	113	36%	17%		9%	-9%	-22%
Total Protein	82/85	-10%	**-7%**	-16%	-7%	-9%	***-13%***
	113	5%	2%		0%	-3%	0%

% relative to controls during on Days 82[a]/85 and 113 (Recovery group); Green denotes %↑; Bold: P ≤ 0.05; Bold and italic: P ≤ 0.01; Bold, italic: *P ≤ 0.001; [a]5/6 surviving males at 1 mg/kg were euthanized early on Day 82, including the recovery animals

Urinalysis	No findings
Gross Pathology	The main findings were within the oral cavity in 0.5 and 1 mg/kg animals, and recovered during the recovery period: • Depressed/dark focus on mucosa of the upper lip, which correlated histologically with erosion/ulcer • Dark/pale abrasions and/or depressed focus on the hard palate mucosa, which correlated histologically with erosion/ulcer • Enlargement of the mandibular lymph node, which correlated histologically with increased lymphoid cellularity
Organ Weights	No findings
Histopathology (Adequate battery: Yes)	Refer to Table 8 for selected histopathology findings. The main target organs included the oral cavity, hard palate, digestive tract, lymph nodes, reproductive tract (females only), skin, eye, larynx, and kidneys (males only).
Other Evaluations	No test article-related neurological abnormalities or changes in respiration rate, body temperature, arterial oxygen saturation, body temperature, or bone marrow smears.
Toxicokinetics	• Mobocertinib, AP32914, and AP32960 exposure increased in an approximately dose-proportional manner in males and females on Day 1 and in males on Days 81/91; and in a greater than dose-proportional manner in females on Day 91.

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- There were no significant sex-related differences in exposure.
- There was no accumulation of mobocertinib or metabolite AP32960. The AR for metabolite AP32914 was 3.16–4.55 in males and 3.70–4.85 in females.

Toxicokinetic Parameters for Mobocertinib

	Males			Females		
mg/kg	**0.25**	**0.5**	**1**	**0.25**	**0.5**	**1**
Day 1						
Tmax (h)	2	2	2	2	2	2
Cmax (ng/mL)	10.6	18.5	35.3	10.8	19.1	42.8
AUC(0-t) (ng·h/mL)	140	257	492	134	244	579
Day 81[a]/91						
Tmax (h)	4	3	4	2	4	4
Cmax (ng/mL)	11.6	26.1	43.1	11.6	23.9	69.0
AUC(0-t) (ng·h/mL)	164	364	638	154	330	1040

[a]Surviving 1 mg/kg male animals were terminated early on Day 82 and blood was collected post-dose on Day 81
h = hours; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

Toxicokinetic Parameters for Metabolite AP32914

	Males			Females		
mg/kg	**0.25**	**0.5**	**1**	**0.25**	**0.5**	**1**
Day 1						
Tmax (h)	8	2	4	3	2	4
Cmax (ng/mL)	0.27	0.50	0.70	0.24	0.50	0.95
AUC(0-t) (ng·h/mL)	2.40	6.75	11.8	2.96	7.21	14.7
Day 81[a]/91						
Tmax (h)	4	4	4	4	4	4
Cmax (ng/mL)	0.53	1.24	1.46	0.51	1.36	3.35
AUC(0-t) (ng·h/mL)	7.78	21.2	24.3	7.78	21.2	62.3

[a]Surviving 1 mg/kg male animals were terminated early on Day 82 and blood was collected post-dose on Day 81
h = hours; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

Toxicokinetic Parameters for Metabolite AP32960

	Males			Females		
mg/kg	**0.25**	**0.5**	**1**	**0.25**	**0.5**	**1**
Day 1						
Tmax (h)	3	2	2	4	4	4
Cmax (ng/mL)	1.63	3.06	6.65	1.54	3.49	7.75
AUC(0-t) (ng·h/mL)	22.0	42.5	94.3	20.2	46.7	106
Day 81[a]/91						
Tmax (h)	3	2	4	2	2	2
Cmax (ng/mL)	2.21	4.15	7.54	2.00	4.86	9.80
AUC(0-t) (ng·h/mL)	26.5	56.0	96.5	23.0	60.4	148

[a]Surviving 1 mg/kg male animals were terminated early on Day 82 and blood was collected post-dose on Day 81
h = hours; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

Table 8: Selected Histopathology Findings (3-Month Study; Dogs)

			Males				Females			
Organ/Tissue	Finding	Dose (mg/kg)	0	0.25	0.5	1	0	0.25	0.5	1
# of Dogs Examined (dosing/recovery)			4/2R	4/2R	4/2R	5*/0R	4/2R	4/2R	4/2R	4/2R
Palate, hard[a]	Erosion/ulcer; focal, multifocal, mucosal, palate	Minimal				1				
		Mild			3	3			1	2
		Moderate				1		1		1
	Hyperplasia; epithelial, palate	Minimal								2
		Mild				1				
		Moderate			4	4		1	2	2
	Inflammation, mixed cell; focal, multifocal, palate	Minimal			2	1			1	
		Mild			2	3		1	1	1
Body cavity, oral[b]	Erosion/ulcer; focal, multifocal, mucosal	Minimal				2				1
		Mild				2				
	Hyperplasia; epithelial	Mild		1/1R						1
		Moderate			1	4			1	1
	Inflammation, mixed cell; mucosal, multifocal, focal	Mild		1R	1	3				2
		Moderate				1				
	Inflammation, neutrophilic; palate	Mild				1				
Thymus	Decreased cellularity; lymphoid	Mild	1/1R		2	4	1	2	2R	
		Moderate		3	1/1R				1	1R
	Hemorrhage; focal, multifocal	Minimal	2/1R	3/2R	3/2R	1	2/1R	4/2R	2/2R	1/2R
Tongue	Decreased thickness; epithelial	Moderate			3	2		2	4	
		Mild				4				4
	Erosion/ulcer; multifocal	Mild								1
	Hyperplasia; focal, epithelial	Mild								1
	Inflammation, neutrophilic; focal, multifocal, epithelial	Minimal				1				1
Esophagus	Atrophy; submucosal, glandular	Minimal		1	1	3				1
		Mild		1		1				1
	Decreased thickness; epithelial	Minimal		2	4	3			1	2
		Mild		2		3				
Kidney	Basophilia; focal, tubular, unilateral	Minimal						1		1R
	Dilatation; tubular, unilateral	Mild				1				
		Moderate				1				
	Hemorrhage; unilateral, interstitial	Mild				1				
	Pigment; multifocal, epithelial, bilateral, cortex	Mild				2				
	Infiltration, mononuclear cell; focal, bilateral, focal, unilateral, multifocal, unilateral	Minimal		1R	1R	1				

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			Males				Females			
Organ/Tissue	Finding	Dose (mg/kg)	0	0.25	0.5	1	0	0.25	0.5	1
# of Dogs Examined (dosing/recovery)			4/2R	4/2R	4/2R	5*/0R	4/2R	4/2R	4/2R	4/2R
Lymph node, mandibular	Erythrocytosis/erythrophagocytosis; bilateral, multifocal, unilateral	Minimal				2	1/1R	1	1/1R	2/1R
	Increased cellularity; bilateral, lymphoid	Mild				2				
		Moderate			1	2				
Cervix	Decreased thickness; epithelial	Min							1	1R
		Mild						3		2
		Moderate						1	3	2
Eye	Decreased thickness; epithelial, diffuse, focal, multifocal	Minimal				1			1	1
		Mild				2				3
Gland, pituitary	Cyst; focal, pars distalis, pars intermedia	Minimal			1	1			2/1R	2
		Moderate				1	2			2
Lung	Hemorrhage; focal, multifocal, alveolar	Mild		1		2				
	Infiltration, mononuclear cells; focal, multifocal, interstitial, multifocal, perivascular	Mild		1R	1R	1				
	Inflammation, mixed cell; multifocal, interstitial,	Moderate				1				
	Inflammation, neutrophilic; multifocal, alveolar	Moderate				1				
Larynx	Decreased thickness; epithelial	Minimal		2	2	1			2	
		Mild		1	2	2			1	4
		Moderate				3				
Lymph node, mesenteric	Erythrocytosis/ erythrophagocytosis	Minimal	2/1R	3/1R	1/1R	1	1	3/1R	3	2
		Mild	1/1R	1/1R	2	3	2/2R	1/1R	1R	2R
		Moderate			1/1R	2			1R	1
		Marked								1
Vagina	Decreased thickness; epithelial	Mild						3		1
		Moderate						1	4	3
Large intestine, rectum	Decreased thickness	Minimal				1			1	1
	Inflammation, mixed cell; adnexa, follicle	Mild		1	1R	1			1/1R	2
Gland, adrenal	Vacuolation; multifocal, bilateral, zona fasciculata/reticularis	Minimal						1/1R	1	1
		Moderate						1		1
Lymph node[c]	Erythrocytosis/ erythrophagocytosis	Marked			1					2R
		Moderate					1R	1R	1	2
Stomach	Edema; mucosal	Mild								1
	Infiltration, mixed cell; non-glandular, cardia	Minimal				2				
Salivary gland, submandibular	Infiltration, mononuclear cell; focal, multifocal	Minimal		1		2	1	1	1R	
	Infiltration, mixed cell; focal	Mild								1

			Males				Females			
Organ/Tissue	Finding	Dose (mg/kg)	0	0.25	0.5	1	0	0.25	0.5	1
# of Dogs Examined (dosing/recovery)			4/2R	4/2R	4/2R	5*/0R	4/2R	4/2R	4/2R	4/2R
Uterus	Atrophy; mucosal	Minimal							1	2
Skin	Inflammation, mixed cell; focal, adnexa	Mild				1				
Spinal cord, cervical	Degeneration; multifocal, axonal	Minimal				1				1/1R
Ureter	Dilatation; unilateral	Moderate				1				

*Includes the three Main Study males and two Recovery males that were euthanized early on Day 82; [a]Zero 0.25 mg/kg males, one 0.25 mg/kg female, and two 0.5 mg/kg females examined; [b]Zero 0.25 mg/kg male and female, one 0.5 mg/kg male and female, and two 1 mg/kg females examined; [c]Only one 0.5 mg/kg male examined from all groups and only two 0.5 mg/kg and 1 mg/kg females examined

General toxicology; additional studies

In rats, mobocertinib administration resulted in histological findings of decreased corneal epithelial thickness in the 4-week repeat-dose toxicology study at doses ≥ 0.8 times the human exposure (AUC) at the 160 mg once daily clinical dose. In the 4-week repeat-dose study in dogs, mobocertinib administration resulted in discharge from the eye, sclera injection, partial or complete closure of the eye and histological findings of corneal epithelial atrophy at doses ≥ 0.3 times the AUC at the 160 mg once daily clinical dose.

5.5.2 Genetic Toxicology

The Applicant's Position:

Mobocertinib was not mutagenic in a GLP-compliant bacterial reverse mutation assay (Ames assay) in the presence and absence of Aroclor 1254-induced rat liver S9 fractions at concentrations up to 5,000 µg/plate. In addition, mobocertinib was not clastogenic in a GLP-compliant in vitro mammalian chromosome aberration assay using human peripheral blood lymphocytes (HPBLs) at concentrations up to 32 µg/mL, which was the highest concentration evaluated based on approximately 50% reduction in cell growth and mobocertinib precipitation at higher concentrations. Mobocertinib did not induce chromosome damage in immature erythrocytes in Sprague-Dawley rats administered mobocertinib once daily by oral gavage for 2 days at 60, 100, 300, and 500 mg/kg.

The FDA's Assessment:

FDA confirmed the Applicant's results of the submitted genotoxicity assays and agrees with the conclusions. Standard positive controls confirmed the sensitivity and validity of these GLP-compliant assays.

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5.5.3 Carcinogenicity

The Applicant's Position:

Carcinogenicity studies were not conducted and are not warranted per ICH S9 guidance for nonclinical safety assessment of pharmaceuticals intended for the treatment of advanced cancer [46].

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not needed to support the use of mobocertinib in the currently proposed indication per ICH S9.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:

Dedicated fertility and early embryonic development studies were not conducted and are not warranted per ICH S9 guidance for nonclinical safety assessment of pharmaceuticals intended for the treatment of advanced cancer [46]. Reproductive organs were weighed and/or examined microscopically in single- and repeat-dose rat and dog toxicity studies. In rats, following repeat administration for up to 3 months, generally reversible reproductive organ changes included decreases in organ weights affecting the seminal vesicle/prostate gland, epididymides, uterus, and/or ovary/oviduct. Microscopic findings included decreased epithelial thickness and/or atrophy in the cervix, vagina or uterus (which precluded estrus staging) in females and atrophy of the prostate gland and mammary gland in males, which correlated with organ weight changes. In repeat-dose toxicity studies in dogs, reversible decreases in ovary weights, with no microscopic correlate, were observed. In addition, generally reversible microscopic changes included atrophy and decreased epithelial thickness in the uterus, cervix, and/or vagina. Changes in testis and epididymis in the 14-day study were considered secondary to decreased food consumption and/or stress, while in the 28-day study changes in the testis and prostate gland were considered related to the immaturity and uneven distribution of immature animals. In the 3-month toxicity study in dogs, there were no reproductive tract effects in the sexually mature males.

In a preliminary GLP-compliant embryo-fetal development study in pregnant rats, once daily administration of mobocertinib by oral gavage at doses of 1.25, 2.5, or 5 mg/kg over Days 6 to 20 post coitum was well-tolerated. At a dose of 10 mg/kg, there was maternal toxicity as evidenced by reduced food consumption and lower body weight and body weight gains, and adverse effects on embryo-fetal development, as evidenced by embryolethality (embryo-fetal death) and effects on fetal growth (decreased fetal weight). There was no clear evidence of teratogenicity (dysmorphogenesis) at any dose. The no-observed-adverse-effect level for maternal toxicity and embryo-fetal development was 5 mg/kg. Based on the embryolethality observed at 10 mg/kg, a definitive embryo-fetal development study was deemed unnecessary and was not conducted.

Prenatal and postnatal development studies were not conducted and are not warranted per ICH S9 guidance for nonclinical safety assessment of pharmaceuticals intended for the treatment of advanced cancer [46].

The FDA's Assessment:

Fertility and Early Embryonic Development

Fertility and early embryonic development studies were not conducted or needed to support the use of mobocertinib in the proposed indication per ICH S9. FDA generally agrees with the Applicant's summary of reproductive tract findings in the toxicology studies except epididymis weight, which was not substantially affected in the 28-day or 3-month toxicology studies.

Embryo-Fetal Development

The Applicant did not submit GLP-compliant embryo-fetal development studies in two species. Rather, consistent with ICH S9, since a GLP-compliant embryofetal development study in rats demonstrated clear positive results at doses resulting in exposures approximately 1.7 times the clinical exposure at the 160 mg human dose, FDA agreed that this study was sufficient to convey the developmental risk to patients. FDA generally agrees with the Applicant's assessment of the embryofetal study, and FDA's assessment is below.

Study title/number: An Oral Preliminary Embryo-fetal Development Study of TAK-788 in Rats/Study Nos. 9001361 and 9001361 Amendment 1

Key Study Findings

- Treatment with 10 mg/kg mobocertinib resulted in reduced maternal food consumption and lower body weight/body weight gains.
- Mobocertinib induced embryo-fetal mortality due to post-implantation loss (early resorptions) as well as decreased fetal weight at 10 mg/kg (approximately 1.7 times the exposure based on AUC at the human dose of 160 mg).
- There was no clear evidence of fetal malformations at the high dose level (10 mg/kg).

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0, 1.25, 2.5, 5, and 10 mg/kg once daily from Gestation Day (GD) 6 to 20
Route of administration:	Oral gavage
Formulation/Vehicle:	25 mM citrate buffer
Species/Strain:	Rat/Sprague-Dawley Crl:CD(SD)
Number/Sex/Group:	8 females/group
Satellite groups:	Toxicokinetic: 8 treated females/group
Study design:	Time-mated rats were administered mobocertinib once on GD 6 to GD 20. Rats were euthanized on GD 21.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	**10 mg/kg:** Increased incidence of thin fur and fur staining starting on GD 9 and GD 16, respectively
Body Weights	**10 mg/kg:** Decrease in maternal body weight by 8% to 13% of control maternal weight from GD 18-21; decrease in corrected (for uterine weight) maternal body weight by 11% of control weight; corrected body weight gain from GD 6-21 decreased by 55% of the control.
Food Consumption	**1.25, 2.5, 5 mg/kg**: Decrease in mean food consumption by 6–15% on GD 6-20 **10 mg/kg:** Decrease in mean food consumption by 11–28% on GD 8-20, which was associated with decreased body weight
Necropsy findings Cesarean Section Data	**10 mg/kg:** Increases in mean total and early resorptions and % post-implantation loss. Decreases in male, female, and total fetal weight by 11% compared to controls.

Cesarean Section Findings (Embryo-fetal development Study; Rats)

Dose (mg/kg)	**0**	**1.25**	**2.5**	**5**	**10**
Exposure multiple		**0.19X**	**0.41X**	**0.83X**	**1.72X**
Pregnancy index (%)	100%	100%	100%	100%	100%
# Mated females	8	8	8	8	8
# Pregnant	8	8	8	8	8
# Dams with live fetuses	8	8	8	8	8
Mean # corpora lutea	16.3	17.0	16.8	16.1	15.9
Mean # implantation sites	14.4	15.3	14.4	15.0	14.6
Mean % pre-implantation loss	11.3%	9.9%	13.6%	6.7%	7.5%
Mean % post-implantation loss	4.4%	3.7%	7.1%	5.9%	17.5%*
Mean # early resorptions	0.6	0.5	1.1	0.9	2.4*
Mean # late resorptions	0	0.1	0	0	0.1
Mean total resorptions	0.6	0.6	1.1	0.9	2.5*
Mean # dead fetuses	0	0	0	0	0
Mean # live fetuses	13.8	14.6	13.3	14.1	12.1
Mean fetal body weight (g)	6.1	5.9	6.1	6.1	5.4*
% change from control		↓2.9	↑0.5	↓0.4	↓10.8
Mean weight of males (g)	6.3	6.0	6.3	6.2	5.6*
% change from control		↓4.6	↓0.7	↓1.6	↓10.7
Mean weight of females (g)	5.9	5.7	6.0	5.9	5.3*
% change from control		↓2.9	↑2.0	↓0.03	↓10.9

*P ≤ 0.05 vs. controls

Necropsy findings Offspring	At ≥1.25 mg/kg, increases in moderate to severe convolution and/or dilatation of the ureters were observed compared to controls. Visceral malformations were seen in one 1.25 mg/kg fetus (interrupted intestine and malpositioned kidneys) and one 5 mg/kg fetus (absent adrenal glands, absent right kidney and right ureter); similar findings were not seen at the high dose level (results not shown in Table below). In response to an Information Request, the Applicant clarified that these two fetuses were initially selected for skeletal examination, but a

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visceral examination was authorized following findings at the external examination.

No dose-related test article-related malformations, external variations, or skeletal variations.

Fetal Malformations and Variations (Embryo-fetal development Study; Rats)

Dose (mg/kg)	**0**	**1.25**	**2.5**	**5**	**10**
Number of Fetuses/Litters Examined	110/8	117/8	106/8	113/8	97/8
External malformations: # of fetuses affected (% of litters)					
Entire Subcutis, Edema - Malformation				1 (12.5%)	
Hindlimb, Right, Malrotated				1 (12.5%)	
Tail, Thread-like		2 (25.0%)			
Anus, Small		2 (25.0%)			
Trunk, Short				1 (12.5%)	
Number of Fetuses/Litters Examined	55/8	59/8	53/8	55/8	50/8
Fixed head malformations: # of fetuses affected (% of litters)					
Eye, Left, Small		1 (12.5%)			
Nasopharynx, Narrow		1 (12.5%)			
Visceral variations: # of fetuses affected (% of litters)					
Lobe, Right medial, Supernumerary		1 (12.5%)			
Ureter, Both, Left, Right, Convoluted		2 (25.0%)	3 (37.5%)	6 (25.0%)	4 (37.5%)
Ureter, Both, Left, Right, Dilatation, Moderate		4 (37.5%)	4 (37.5%)	9 (50.0%)	5 (37.5%)
Ureter, Left, Right Dilatation, Severe		2 (25.0%)	2 (25.0%)		2 (25.0%)
Number of Fetuses/Litters Examined	55/8	58/8	53/8	58/8	47/8
Skeletal malformations: # of fetuses affected (% of litters)					
Rib, L2, Fused				1 (12.5%)	
Rib, R2, Fused				1 (12.5%)	
Rib, R6, R2, L2, Fused				1 (12.5%)	
Caudal vertebra, 1 or more, Absent		1 (12.5%)			
Lumbar centrum, 1, Absent		1 (12.5%)			
Lumbar vertebrae, 2–6, Absent		1 (12.5%)			
Sacral vertebrae, 1–4, Absent		1 (12.5%)			
Number of Fetuses/Litters Examined	55/8	58/8	53/8	58/8	47/8
Skeletal variations: # of fetuses affected (% of litters)					
Forepaw phalanges, B4, Incomplete ossification				1 (12.5%)	
Frontal, Both, Incomplete ossification				1 (12.5%)	
Parietal, Right, Incomplete ossification			1 (12.5%)		
Zygomatic arch, Both, Incomplete ossification				1 (12.5%)	
Sternebra, 1, 2, 3, 4, Incomplete ossification				1 (12.5%)	
Sternebra, 5, Misshapen			1 (12.5%)		
Sternebra, 6, Incomplete ossification				1 (12.5%)	1 (12.5%)
Cervical, 7, Short				1 (12.5%)	
Lumbar arch, B1, Isolated ossification site		1 (12.5%)	4 (12.5%)	2 (25.0%)	1 (12.5%)
Lumbar arch, L1, Incomplete ossification			1 (12.5%)		
Lumbar arch, R1, Isolated ossification site		1 (12.5%)	4 (50.0%*)		
Thoracic centrum, 1, Incomplete ossification		1 (12.5%)		2 (25.0%)	
Thoracic centrum, 2, 3, 4, 6, 7 Unossified				1 (12.5%)	
Thoracic centrum, 5, Incomplete ossification				1 (12.5%)	

*P ≤ 0.05 vs. controls; % per litter = (Total # of litters with malformation or variation / Total # of litters) x 100

Toxicokinetics	• Mobocertinib exposure (AUC and C_{max}) increased in a generally dose-proportional manner on GD 6 and GD 20. • For AP32914 and AP32960 metabolites, AUC increased in a greater than dose-proportional manner and C_{max} increased in a generally dose-proportional manner on both days. • There was minimal accumulation (≤1.7-fold) of mobocertinib or metabolite AP32914, but ARs ranged from 4.73 to 8.21 for metabolite AP32960.

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Summary of Toxicokinetic Parameters for Mobocertinib

Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	T_{max} (h)
GD 6	1.25	7.7	107	8
	2.5	17.2	239	4
	5	34.6	473	4
	10	79.0	1000	4
GD 20	1.25	12.9	185	8
	2.5	27.2	394	4
	5	55.5	787	4
	10	134	1640	4

h = hours; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

Summary of Toxicokinetic Parameters for Metabolite AP32914

Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	T_{max} (h)
GD 6	1.25	0.8	3.5	8
	2.5	2.3	28.9	8
	5	4.1	55.2	8
	10	8.3	117	8
GD 20	1.25	0.6	2.4	8
	2.5	1.4	18.7	8
	5	2.8	40.0	8
	10	5.9	80.6	8

h = hours; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

Summary of Toxicokinetic Parameters for Metabolite AP32960

Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	T_{max} (h)
GD 6	1.25	0.4	NR	4
	2.5	1.3	5.9	8
	5	2.1	29.1	8
	10	4.5	58.5	4
GD 20	1.25	1.4	20.5	8
	2.5	3.5	48.2	4
	5	9.4	138	8
	10	22.3	340	4

h = hours; NR = Not reportable, due to < 3 consecutive concentrations; AUC(0-t) = AUC from start of dose administration to the time after dosing at which the last quantifiable concentration was observed (up to 24 hours)

5.5.5 Other Toxicology Studies

Applicant's Position:

Mobocertinib did not demonstrate phototoxic potential in a GLP-compliant in vitro assay with mouse fibroblasts exposed to up to 100 µg/mL mobocertinib in the presence or absence of ultraviolet radiation (UVR). In a 14-day oral qualification study in rats, administration of mobocertinib at a dose of 10 mg/kg alone or containing ML00952187(mobocertinib/ML00952187), a process intermediate, at 0.165 mg/kg (1% of the 160 mg clinical dose) once daily via oral gavage for 14 days was tolerated by rats and did not adversely affect the overall health or condition of the animals. There were no differences in mobocertinib or metabolite maximum concentrations or exposures between the mobocertinib or mobocertinib/ML00952187 dose groups. Target organ toxicities included effects on the digestive tract, male and female reproductive tract, skin, eyes, lymph nodes, spleen, and bone marrow. Administration of mobocertinib alone or in combination with ML00952187 resulted in effects that were comparable in incidence and severity. The only notable exceptions, which were increased in incidence and severity in animals given mobocertinib alone, were increased cellularity in the bone marrow, seminiferous tubule degeneration in the testes, and reduced sperm with cellular debris in the epididymis.

The FDA's Assessment:

FDA confirmed the Applicant's results of the submitted phototoxicity assay and agrees with the conclusions. FDA did not review the 14-day oral qualification study in rats because it was not warranted based on discussions with the Product Quality review team. Thus, the Applicant's conclusions from this study were not verified by the FDA.

Study title/number: Neutral Red Uptake Phototoxicity Assay of TAK-788 in BALB/c 3T3 Mouse Fibroblasts/Study No. 20165734

Key Study Findings:

- Mobocertinib did not demonstrate phototoxic potential (Photoirritancy Factor [PIF] = 1.510 and 1.380 in two assays) compared to the positive control promethazine (PIF = 173.199) under the conditions of this in vitro assay. The criterion for "phototoxic" is PIF > 5.
- The performance of the positive control confirmed the sensitivity and validity of the study.

GLP compliance: Yes

Test system: BALB/c 3T3 mouse fibroblasts exposed to mobocertinib (up to 100 µg/mL) in the absence and presence of ultraviolet radiation

Study is valid: Yes

Reference ID: 4857343

X	X
Kelie Reece Primary Reviewer	Emily Wearne Team Leader

Reference ID: 4857343

6.0 CLINICAL PHARMACOLOGY

6.1 Executive Summary

The FDA's Assessment:

Mobocertinib (TAK-788 or AP32788) is an irreversible tyrosine kinase inhibitor for epidermal growth factor receptor (EGFR) and is reported to have higher binding affinity to EGFR exon 20 insertion mutants. The proposed indication for mobocertinib is for the treatment of adult patients with EGFR exon 20 insertion mutation–positive metastatic non–small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have received prior platinum-based chemotherapy. The Applicant's proposed dosage regimen in 160 mg administered orally once daily without regard to food.

The proposed dosage was the maximum tolerated dose of 160 mg QD and was selected from the dose finding portion of study AP32788-15-101. FDA deems the proposed dose adequately justified.

The clinical pharmacology key review questions focused on the adequacy of the proposed dosing regimen for the general patient population, dose recommendations for patients with hepatic impairment, and determining the drug-interaction potential for mobocertinib and its active metabolites as a substrate and a perpetrator.

Post marketing requirements and commitments were agreed to for addressing review issues.

6.1.1 Recommendations

The Clinical Pharmacology review team has reviewed the information contained in NDA 215310 and recommends approval. The key review issues with specific recommendations and/or comments are summarized in Table 9 below.

Table 9: Summary of key review issues and recommendations for NDA 215310

Review Issues	Recommendations and Comments
Pivotal Evidence of Effectiveness	Study AP32788-15-101 part 3 – Single arm study of the safety, pharmacokinetics, and anti-tumor activity of the oral EGFR/HER2 inhibitor TAK-788 in patients with NSCLC The efficacy data set comprises 114 patients with patients with EGFR exon 20 insertion mutation positive NSCLC
General Dosing Instructions	The recommended dosage is 160 mg administered orally once daily without regard to food

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Dosing in patient subgroups (intrinsic factors)	There is no recommended dose adjustment for age, sex, body weight, race, mild or moderate renal impairment, and mild or moderate hepatic impairment
Drug Interactions	Labeling will include instructions to • Avoid coadministration of mobocertinib and strong CYP3A inhibitors • Avoid coadministration of mobocertinib and moderate CYP3A inhibitors. If the concomitant use of moderate CYP3A inhibitors cannot be avoided, dose reduce mobocertinib by 50% with additional electrocardiogram monitoring • Avoid coadministration of mobocertinib and strong and moderate CYP3A inducers • Avoid concomitant use of mobocertinib with hormonal contraceptives and other CYP3A substrates, where minimal concentration changes of the CYP3A substrate may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the FDA approved product package insert.
QTc Assessment	At the recommended dosage, mean increases in the QTc interval of 23 msec (UCL: 26 msec) were detected and mobocertinib treatment is associated with a concentration-dependent QTc prolongation effect.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to FDA revisions to the labeling.
Bridge between the to-be-marketed and clinical trial formulations	Three capsule formulations were used in the clinical pharmacology studies (DiC-A, DiC-B, and DiC-C). DiC-C is the to-be-marketed formulation. The Applicant conducted a relative bioavailability clinical study to bridge between DiC-A and DiC-B (study 1001 part 3). Additional PK comparability between DiC-A and DiC-C was confirmed by pooled PK analysis.

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6.1.2 Post Marketing Requirements and Commitments

The rationale and description of post marketing requirements (PMRs) are detailed in Table 10. Two PMRs are issued to further characterize the pharmacokinetics and safety of oral mobocertinib in subjects with moderate or severe hepatic impairment and severe renal impairment, respectively. Additionally, a third PMR was issued to assess the effect of mobocertinib and its active metabolites on the pharmacokinetics of a breast cancer resistance protein (BCRP) substrate to determine appropriate dosage recommendations when mobocertinib is administered concomitantly with BCRP substrates.

Table 10: Rationale and description of post-marketing requirements for NDA 215310

Post Marketing Requirement -1	
(b) (4)	
PMR description	Conduct a renal impairment clinical trial to evaluate the pharmacokinetics and safety of mobocertinib in patients with normal renal function and patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Draft Guidance for Industry titled: "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing."
Post Marketing Requirement -2	
(b) (4)	
PMR Description	Conduct a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of mobocertinib in patients with normal hepatic function and patients with moderate and severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

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Post Marketing Requirement -3	
	(b) (4)
PMR Description	Conduct a study to assess the effect of mobocertinib and its active metabolites on the pharmacokinetics of a breast cancer resistance protein (BCRP) substrate to determine appropriate dosage recommendations when mobocertinib is administered concomitantly with BCRP substrates. Design and conduct the assessment in accordance with the FDA Guidances for Industry titled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" and/or "Physiologically Based Pharmacokinetic Analyses — Format and Content".

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

Not Applicable

The Applicant's Position:

The clinical pharmacology of mobocertinib and its active metabolites, AP32960 and AP32914, has been thoroughly characterized. The data included in the dossier encompasses the pharmacokinetic (PK) properties following single-and multiple-dose administration of mobocertinib in patients with non-small cell lung cancer (NSCLC) and following single-dose administration in healthy subjects. A total of 6 clinical studies have contributed to the characterization of the clinical pharmacology of mobocertinib (Table 7.a). In addition, 3 dedicated clinical pharmacology studies are ongoing at the time of this submission.

In vitro studies and dedicated in vivo clinical pharmacology studies have been conducted to evaluate drug-drug interaction (DDI) potential, relative bioavailability, food effect (ie, low-fat meal and high-fat meal), absolute bioavailability, and the mass balance of mobocertinib. Additionally, intrinsic and extrinsic factors that may affect the clinical pharmacology of

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mobocertinib were assessed by integrated population PK and physiologically-based PK (PBPK) analyses of relevant data collected from clinical studies across the development program. A concentration-QTc analysis was performed using time-matched PK and triplicate ECG data from Parts 1 and 2 of Study AP32788-15-101, and an analysis was conducted using applicable data from Study AP32788-15-101 to evaluate exposure-response relationships for efficacy and safety to support the benefit/risk profile of the proposed 160 mg QD mobocertinib dose in the target population.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the clinical pharmacology program supports use of mobocertinib (TAK-788 or AP32788) for the treatment of EGFR exon 20 insertion mutation–positive metastatic NSCLC at the Applicant-proposed dosage of 160 mg once daily (QD), without regard to food.

There are three clinical pharmacology post marketing requirements (PMRs) issued by FDA. Two of the PMRs are to conduct and submit the final study reports for the ongoing hepatic and renal impairment studies, respectively. The third PMR is to assess the effect of mobocertinib and its active metabolites on the pharmacokinetics (PK) of a breast cancer resistance protein (BCRP/ABCG2) substrate.

The clinical pharmacology program for the NDA includes the following assessments supported by a total of six completed clinical studies at initial submission, four in healthy subjects without cancer and two in patients with cancer (see below). Three clinical pharmacology studies were ongoing at the time of the NDA submission; the final study reports for one (Study 1004) were submitted during the review cycle and topline results for another (Study 1008) were made available during the review cycle.

- Dose selection/ Dose confirmation:
  - **AP32788-15-101** – Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in patients with Non-Small Cell Lung Cancer

- Drug Interactions
  - **TAK-788-1006** - Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects
    - Part 1 – 20 mg single oral dose mobocertinib; 200 mg multiple dose itraconazole
    - Part 2 – 160 mg single oral dose mobocertinib; 600 mg multiple dose rifampin

  - **Study TAK-788-1004 (Final clinical study report submitted during review cycle)** - Open-Label, Multicenter, Drug-Drug Interaction Study of

TAK-788 and Midazolam, a Sensitive CYP3A Substrate, in Patients with Advanced Non–Small Cell Lung Cancer

- 3 mg single oral- and 1 mg single intravenous (IV)-dose of midazolam; 160 mg single dose mobocertinib

- Food Effect, Absolute and Relative BA/BE
  - **TAK-788-1001** - Randomized, Double-blind, Placebo-Controlled, Single Rising Dose Study to Evaluate Pharmacokinetics, Safety, and Tolerability of TAK-788 Followed by Open-Label, Crossover Evaluation of the Effects of a Low-Fat Meal on TAK-788 Pharmacokinetics and Evaluation of Relative Bioavailability of TAK-788 Capsules in Healthy Subjects

  - **TAK-788-1005** - Randomized, 2-Period, 2-Sequence, Crossover Study to Evaluate the Effect of High-Fat Meal on TAK-788 Pharmacokinetics in Healthy Adult Subjects

  - **TAK-788-1002** - Assess Absolute Bioavailability of TAK-788 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [14C]-TAK-788 in Male Healthy Subjects

- PK, Mass Balance
  - **TAK-788-1001 -** Randomized, Double-blind, Placebo-Controlled, Single Rising Dose Study to Evaluate Pharmacokinetics, Safety, and Tolerability of TAK-788 Followed by Open-Label, Crossover Evaluation of the Effects of a Low-Fat Meal on TAK-788 Pharmacokinetics and Evaluation of Relative Bioavailability of TAK-788 Capsules in Healthy Subjects

  - **TAK-788-1002** - Study to Assess Absolute Bioavailability of TAK-788 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [14C]-TAK-788 in Male Healthy Subjects

  - **TAK-788-1003** - Study of the Oral EGFR/HER2 Inhibitor TAK-788 in Japanese Patients with Non-Small Cell Lung Cancer

  - **AP32788-15-101 -** Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Patients with Non-Small Cell Lung Cancer

- Renal and Hepatic Impairment
  - **Study TAK-788-1007 (ongoing)**: Pharmacokinetic Study of Oral Mobocertinib in Subjects with Severe Renal Impairment and Normal Renal Function

- **Study TAK-788-1008 (ongoing, topline results for subjects with moderate hepatic impairment were available during this review cycle)**: Pharmacokinetics and Safety Study of Oral Mobocertinib in Subjects with Moderate or Severe Hepatic Impairment and Normal Hepatic Function

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:

Data from the Pooled Prior Platinum Analysis Set of Study AP32788-15-101 demonstrated that a mobocertinib dose of 160 mg QD was effective at achieving durable confirmed objective responses. In addition, mobocertinib at a dose of 160 mg QD presents a manageable safety profile typical of next generation EGFR TKIs, and treatment-emergent adverse events were clinically manageable. A total of 75% of patients in the Pooled Prior Platinum Analysis Set were able to continue treatment at the starting dose of 160 mg mobocertinib without a dose reduction due to an adverse event.

In the exposure-efficacy analyses, systemic exposure was not a statistically significant predictor of ORR. This suggests that the efficacy benefit of mobocertinib was consistent across the range of exposures achieved with the 160 mg QD regimen. Although systemic exposure was not a statistically significant predictor of the treatment-emergent adverse events evaluated, the final exposure-safety models suggested a reduction in the odds of experiencing these treatment-emergent adverse events as the odds ratios associated with a change in exposure corresponding to a dose reduction from 160 mg to 120 mg QD were less than 1. In addition, no discernible relationship was identified between systemic exposure and the time to the first mobocertinib dose reduction. The exposure-response analyses collectively support a favorable benefit/risk profile of the mobocertinib 160 mg QD regimen.

Mobocertinib may be taken with or without food because the food effect studies demonstrated that a low-fat meal or high-fat meal had no clinically meaningful effect on the combined molar exposure (C_{max} and AUC_{∞}) of mobocertinib, AP32960, and AP32914, as the 90% CIs for the geometric mean ratios for C_{max} and AUC_{∞} were contained completely within the 80% to 125% equivalence limits.

The Applicant's Position:

The available data support the proposed recommended dosing regimen of 160 mg QD mobocertinib, with or without food, for the treatment of patients with previously treated NSCLC harboring *EGFR Exon 20* insertion mutations.

The FDA's Assessment:

FDA agrees that the proposed dosing of 160 mg QD is adequately justified by the data and analyses included in the NDA based on the following:

1. As of August 2018, from parts 1 and 2 of study AP32788-15-101, the single best objective response rate (ORR) at 160 mg QD in patients whose tumors harbored EGFR exon 20 insertion mutations was 47.6% (N = 21). This ORR rate is numerically higher than the ORR observed for patients whose tumors harbored EGFR exon 20 insertion mutations at 120 mg QD (33.3%; N = 9). At the later data cutoff date of June 2019, the best ORR at 160 mg QD was 50% (N = 28) and remained numerically higher than 120 mg QD (19%; N = 21). Of note, 160 mg QD was the maximum tolerated dose (MTD) (Source: EDR Integrated Summary of Safety Table 18.1.1.5.1).

2. A positive trend between total molar concentration (nM.hr/day) of mobocertinib and its active metabolites and best confirmed clinical response (probability of CR +PR) in 114 patients with patients with EGFR exon 20 insertion mutation positive NSCLC (the efficacy data set) was observed. Of note, this positive trend is only based on the exposure from a single dose level (160 mg QD) in Study AP32788-15-101 See section 18.3.1 Population PK review.

3. The mean mobocertinib dose intensity (standard deviation, SD) for the safety dataset (all patients who received 160 mg QD (N=256)) was 134.60 mg/day (29.650). The median dose intensity for the same population was 150.32 mg/day, suggesting the proposed dosing regimen was generally well tolerated. Specifically, 69% of patients did not dose reduce and 82% did not discontinue dosing due to adverse reactions (ARs), indicating the majority of patients did not dose reduce or discontinue due to ARs. See Section 8.2 - Review of Safety for additional details.

4. Positive trends between total molar concentration (nM.hr/day) of mobocertinib and its active metabolites and 1) probability of occurrence of Grade 3 and higher adverse reactions (ARs), 2) drug-related Grade 3 and higher ARs, 3) serious adverse reactions (SARs), and 4) Grade 3 and higher diarrhea among patients who received mobocertinib were observed based on exposures ranging from 3% to 113 % of the recommended dosage mg QD (N=295). Of note, the positive trend for exposure-response (ER) for safety is consistent across different exposure metrics (total sum of molar concentration, parent molar concentration or metabolites molar concentration). As such, FDA used total molar exposure for analyses and dose adjustment recommendations. The positive ER trend for safety supports the Applicant's proposed dose reductions due to ARs See Section 18.3.1- Population PK review.

5. Of the 31% of patients (N=79) who did dose reduce, 80 percent experienced resolution of their ARs after dose reduction to 120 mg QD. Among patients whose ARs did not resolve at 120 mg QD, 79 percent had resolution of their AR(s) with further dose reduction to 80 mg QD, suggesting the dose reduction scheme can adequately manage ARs. See section 8.2 Review of Safety.

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6. Total $Cmax_{ss}$ at 160 mg QD (70.4 ng/mL) in patients was within the range of Cmax in patient-derived xenograft mouse models where tumor growth was inhibited 89% (117 ng/mL). Of note, total $Cmax_{ss}$ at 120 mg QD (52.7 ng/mL) in patients was lower than 160 mg QD but also within the range where patient-derived xenograft mouse model tumor growth was inhibited 56% (31 ng/mL). See Section 5 - Nonclinical Pharmacology/ Toxicology.

FDA also agrees with the Applicant's proposed dosage of mobocertinib 160mg QD to be administered without regard to food. This is based on the observed lack of clinically significant effect of high- or low-fat meals on mobocertinib exposure. Specifically, the least squared mean (LSM) ratio (90% CI) of the combined molar Cmax and AUC_{inf} of mobocertinib and its active metabolites for high-fat meal versus fasted was 0.970 (0.910-1.05) and 1.13 (1.07-1.20), respectively. The LSM ratio (90% CI) of the combined molar Cmax and AUC_{inf} of mobocertinib and its active metabolites for low-fat meal versus fasted was 0.948 (0.835-1.08) and 0.943 (0.867-1.03), respectively. See Table 11.

Of note, gastrointestinal (GI) toxicity was the most frequent AR, with 93 percent of patients experiencing diarrhea of any toxicity grade. There were positive trends for relationships between exposure and the occurrence of Grade 3 and higher adverse reactions (ARs), drug-related Grade 3 and higher AR, serious adverse reactions (SARs), and Grade 3 and higher diarrhea (see #4 above), suggesting that the observed GI toxicity is associated with systemic mobocertinib exposure, rather than a local effect in the gastrointestinal tract. As such, administration of mobocertinib with food is not likely to ameliorate these ARs.

Additionally, a cohort study of 100 patients from Study AP32788-15-101 was used to evaluate the effect of 'fasted' vs 'with or without a low-fat meal' and incidence of GI toxicity (diarrhea, nausea, vomiting). The rate of dose disruption due to GI toxicity were generally comparable between the two cohorts. See Table 11. Specifically, 98% of patients who received 160 mg QD mobocertinib on an empty stomach experienced GI toxicity, which is similar to the 96% incidence of GI toxicity observed in patients who received 160 mg QD with or without a low-fat meal. Of note, the 'with or without a low-fat meal' cohort did not identify which patients who did or did not receive a low-fat meal; however, the results are supportive and replicate administration without regard to food, as is recommended by the Applicant.

Table 11: Summary of findings from food effect Studies 1001 and 1005

Study Number	Study Objective	Pharmacokinetic parameter	LS Geometric Mean Ratio (90% CI) Test/ Fasted
1001	Assessment of the effect of a **low-fat meal** on mobocertinib PK	Cmax (ng/mL)	0.964 (0.836-1.11)
		AUCinf (h ng/mL)	0.951 (0.874-1.03)
		Combined molar Cmax (nM)	0.948 (0.835-1.08)
		Combined molar AUCinf (h ng/mL)	0.943 (0.867-1.03)
1005	Assessment of the effect of a **high-fat meal** on mobocertinib PK	Cmax (ng/mL)	1.02 (0.960-1.09)
		AUCinf (h ng/mL)	1.22 (1.14-1.31)
		Combined molar Cmax (nM)	0.970 (0.910-1.05)
		Combined molar AUCinf (h ng/mL)	1.13 (1.07-1.20)

Source: EDR - Study TAK-788-1001 CSR Table 11.n and Study TAK-788-1005 CSR Table 11.j and Table 11.k.

Table 12: Summary of findings from cohort study of 100 patients from Study 101 evaluating the effect of "fasted" vs. "with or without low-fat meal" and incidence of GI toxicity

Cohort	Preferred Term	TEARs N (%)	Grade 3 and higher N (%)	Dose Reduction N (%)	Dose Interruption N (%)	Dose Discontinuation N (%)
Patients receiving 160 mg QD **on an Empty Stomach** (n=50)	Any GI Toxicities	49 (98)	15 (30)	11 (22)	21 (42)	6 (12)
	Diarrhea	46 (92)	13 (26)	9 (18)	16 (32)	4 (8)
Patients receiving 160 mg QD **with or without a low-fat meal** (n=50)	Any GI Toxicities	48 (96)	14 (28)	7 (14)	13 (26)	4 (8)
	Diarrhea	47 (94)	13 (26)	6 (12)	9 (18)	2 (4)

Source: Applicant Response to Information Request received 30Apr2021 (EDR Submission 20 under NDA 215310)

6.2.2.2 Therapeutic Individualization

Data:

The effect of intrinsic and extrinsic factors on the PK of mobocertinib and its active metabolites was assessed during development. The key results are summarized below.

Intrinsic Factors

The population PK analysis demonstrated that age (18 to 86 years), sex, body weight (37.3 kg to 132 kg), and race do not affect the PK of mobocertinib and its active metabolites. Therefore, no dose adjustment is required for these intrinsic factors.

- *Patients with Hepatic Impairment:*

During clinical development, patients were allowed to enroll in clinical studies if their total bilirubin was ≤1.5 times the upper limit of normal (ULN) and their aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were ≤2.5 times the ULN. Accordingly, patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (ie, total bilirubin ≤ULN and AST or ALT >ULN or total bilirubin >1-1.5 times ULN and any AST or ALT), were included in clinical studies. Bilirubin, ALT, and AST were not identified as statistically significant covariates in the population PK analysis. This suggests that no dose adjustment is necessary for patients with mild hepatic impairment. The effect of moderate and severe hepatic impairment on the PK of mobocertinib and its active metabolites is being evaluated in the ongoing Study TAK-788-1008.

- *Patients with Renal Impairment:*

Patients with mild or moderate renal impairment have been included in clinical studies conducted during the development of mobocertinib. In the population PK analysis, creatinine clearance (26.3 to 251 mL/min) and estimated glomerular filtration rate (33.6 to 304 mL/min/1.73 m^2) were not identified as significant covariates, thereby indicating that the PK of mobocertinib and its active metabolites is similar in patients with normal renal function, mild renal impairment, or moderate renal impairment (ie, creatinine clearance ≥30 mL/min; estimated glomerular filtration rate ≥30 mL/min/1.73 m^2). Consequently, no dose adjustment is required for patients with mild or moderate renal impairment. The effect of severe renal impairment on the PK of mobocertinib and its active metabolites is being evaluated in the ongoing Study TAK-788-1007.

Extrinsic Factors

- *Effect of Other Drugs on Mobocertinib*

The results of in vitro studies indicate that mobocertinib, AP32960, and AP32914 are predominantly metabolized by CYP3A. Therefore, clinical Study TAK-788-1006 evaluated the effect of a strong CYP3A inhibitor (itraconazole) and strong CYP3A inducer (rifampin) on the single-dose PK of mobocertinib and its active metabolites, AP32960 and AP32914. Additionally, a PBPK analysis was performed to further assess the effect of strong, moderate, and weak CYP3A inhibitors, and strong and moderate CYP3A inducers, on the single- and multiple-dose PK of mobocertinib and its active metabolites.

When mobocertinib was coadministered with itraconazole (Study TAK-788-1006 Part 1), the combined molar C_{max} and AUC_{∞} of mobocertinib, AP32960, and AP32914 were approximately 186% and 527% higher, respectively, in the presence of itraconazole than when mobocertinib was administered alone, with a least-squares geometric mean ratio (90% CI) for C_{max} of 2.86

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(2.48, 3.30) and AUC_∞ of 6.27 (5.20, 7.56). In the PBPK analyses, after multiple-dose administration of 160 mg QD mobocertinib, the model-predicted geometric mean steady-state AUC ratios for combined molar exposure of mobocertinib, AP32960, and AP32914 with versus without coadministration of strong, moderate, or weak CYP3A inhibitors were approximately 5 (itraconazole, 5.19; ketoconazole, 4.74), approximately 2 (fluconazole, 2.35; erythromycin, 2.16), and 1.16 (cimetidine), respectively. Therefore, the concomitant use of strong and moderate CYP3A inhibitors with mobocertinib should be avoided. If the concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of mobocertinib should be reduced by approximately 50% (eg, from 160 mg to 80 mg, 120 mg to 40 mg, or 80 mg to 40 mg, based on the available capsule strengths). No dose adjustment is needed when mobocertinib is coadministered with weak CYP3A inhibitors.

In the clinical Study TAK-788-1006 Part 2, the combined molar C_{max} and AUC_∞ of mobocertinib, AP32960, and AP32914 were reduced in the presence of rifampin by approximately 92% and 95%, respectively, corresponding least-squares geometric mean ratios (90% CI) of 0.08 (0.07, 0.11) and 0.05 (0.04, 0.07), respectively. In the PBPK analyses, after multiple-dose administration of 160 mg QD mobocertinib, the model predicted that the strong CYP3A inducer rifampin may reduce the steady-state combined molar AUC of mobocertinib, AP32960, and AP32914 by >90% (geometric mean ratio of 0.08). An approximately 60% decrease (geometric mean AUC ratio of 0.42) in steady state combined molar AUC of mobocertinib, AP32960, and AP32914 was predicted in the presence of the moderate CYP3A inducer, efavirenz. As a result, the concomitant use of strong and moderate CYP3A inducers with mobocertinib should be avoided. If the concomitant use of moderate CYP3A inducers cannot be avoided, the dose of mobocertinib should be gradually increased in 40 mg increments after 7 days of treatment with mobocertinib and the moderate CYP3A inducer, as tolerated, up to a maximum of twice the mobocertinib dose that was tolerated prior to the initiation of the moderate CYP3A inducer.

- *Effect of Mobocertinib on Other Drugs*

In vitro studies indicate that mobocertinib, AP32960, and AP32914 are reversible inhibitors of CYP2B6, CYP2C8, and CYP3A. In addition, mobocertinib, AP32960, and AP32914 were mechanism-based inhibitors of CYP3A in vitro. In human hepatocytes, mobocertinib, AP32960, and AP32914 were potent inducers of CYP3A. Thus, mobocertinib and its metabolites may have the potential for PK drug interactions with CYP substrates, particularly substrates of CYP3A. As a result, the ongoing clinical Study TAK-788-1004 is evaluating the effect of multiple-dose 160 mg QD mobocertinib administration on the PK of orally and intravenously administered midazolam, a sensitive CYP3A substrate.

In the PBPK analyses, no clinically meaningful DDIs were predicted following coadministration of multiple doses of 160 mg QD mobocertinib with probe substrates of CYP2B6, CYP2C8, and CYP2C9 as coadministration of mobocertinib resulted in a less than 15% change in the AUC of the probe substrate for each CYP isozyme. Therefore, administration of mobocertinib is not expected to result in clinically meaningful inhibition of CYP2B6, CYP2C8, and CYP2C9 in vivo. For the CYP3A probe substrates, alprazolam and midazolam, the PBPK analyses predicted

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geometric mean AUC and C_{max} ratios with versus without mobocertinib coadministration of 0.82 and 0.98 for alprazolam, and 0.63 and 0.70 for midazolam, respectively. Consequently, the PBPK analyses predicted a net weak induction effect on CYP3A activity following mobocertinib administration, which is consistent with the autoinduction observed with the 160 mg QD mobocertinib dose in Study AP32788-15-101.

Taken together, the available data indicate that mobocertinib may reduce plasma concentrations of coadministered medications that are predominantly metabolized by CYP3A. The concomitant use of mobocertinib with CYP3A substrates can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates. Mobocertinib may also induce other enzymes and transporters (eg, CYP2C, P-glycoprotein [P-gp]) via the same mechanisms responsible for induction of CYP3A (eg, pregnane X receptor activation).

- *Transporter-Based Interactions:*

Mobocertinib is an in vitro inhibitor of P-gp and breast cancer resistance protein (BCRP). However, the PBPK model predicted no clinically meaningful effect of multiple-dose administration of 160 mg QD mobocertinib on the PK of probe substrates for P-gp or BCRP (probe substrate geometric mean C_{max} and AUC ratios with versus without mobocertinib of 1). Therefore, mobocertinib is not expected to result in clinically meaningful inhibition of P-gp or BCRP in vivo.

Mobocertinib is not an in vitro inhibitor of organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, or organic cation transporter (OCT) 2. Mobocertinib inhibited multidrug and toxin extrusion protein (MATE) 1, MATE2-K, and OCT1 in vitro. However, the potential for in vivo inhibition of these transporters is inferred to be low.

Mobocertinib is not a substrate of OATP1B1 or OATP1B3. Mobocertinib, AP32960, and AP32914 were in vitro substrates for P-gp. Mobocertinib and AP32914 were not BCRP substrates in vitro; however, AP32960 may be a weak BCRP substrate. Given that mobocertinib exhibits high solubility and high permeability in vitro, P-gp inhibitors are unlikely to increase plasma concentrations of mobocertinib.

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

Therapeutic individualization is not needed for the intrinsic factors of age, sex, race, body weight, mild hepatic impairment, and mild-to-moderate renal impairment. In addition, mobocertinib administration is not expected to result in clinically meaningful inhibition of CYP2B6, CYP2C8, CYP2C9, P-gp, BCRP, MATE1, MATE2-K, and OCT1 in vivo. P-gp inhibitors are unlikely to increase plasma concentrations of mobocertinib.

To account for potential drug-drug interactions, the following dosage modifications are recommended:

- The concomitant use of strong and moderate CYP3A inhibitors with mobocertinib should be avoided. If the concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of mobocertinib should be reduced by approximately 50% (eg, from 160 mg to 80 mg, 120

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mg to 40 mg, or 80 mg to 40 mg, based on the available capsule strengths). No dose adjustment is needed when mobocertinib is coadministered with weak CYP3A inhibitors.

- The concomitant use of strong and moderate CYP3A inducers with mobocertinib should be avoided. If the concomitant use of moderate CYP3A inducers cannot be avoided, the dose of mobocertinib should be gradually increased in 40 mg increments after 7 days of treatment with mobocertinib and the moderate CYP3A inducer, as tolerated, up to a maximum of twice the mobocertinib dose that was tolerated prior to the initiation of the moderate CYP3A inducer.
- Mobocertinib may reduce plasma concentrations of coadministered medications that are predominantly metabolized by CYP3A. The concomitant use of mobocertinib with CYP3A substrates can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates. Mobocertinib may also induce other enzymes and transporters (eg, CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (eg, pregnane X receptor activation).

The FDA's Assessment:

Intrinsic Factors

Of note, different exposure metrics of mobocertinib and its active metabolites are directly proportional (e.g., total sum of molar concentration, parent molar concentration or metabolites molar concentration). As such, the FDA used total molar exposure for analysis and dose adjustment recommendations. See Section 18.3.1 Population PK review.

The FDA agrees with the Applicant's population PK analysis, where age (18-86 yrs), sex (183 male, 244 female), race (283 White, 19 Black, 115 Asian), body weight (37-132 kg), mild or moderate renal impairment (178 mild, 30 moderate) and mild hepatic impairment (54 mild) did not demonstrate clinically significant effects on the PK of mobocertinib. See Section 18.3.1 Population PK review.

Top line results for moderate hepatic impairment from Sudy 1008 were submitted during this review cycle (N=6). The GMRs (90% CIs) for the combined molar Cmax and AUC last of mobocertinib, AP32960, and AP32914 were 0.848 (0.5779-1.243) and 0.928 (0.6862-1.256), respectively. As such, FDA does not recommend a dose adjustment for patients with moderate hepatic impairment.

- Moderate and Severe Hepatic Impairment

The effect of moderate and severe hepatic impairment on the PK of mobocertinib and its active metabolites is being evaluated in the ongoing Study TAK-788-1008. A PMR was issued for the final study report. See Section 6.1.2 Post Marketing Requirements and Commitments.

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- Severe Renal Impairment

The effect of severe renal impairment on the PK of mobocertinib and its active metabolites is being evaluated in the ongoing Study TAK-788-1007. A PMR was issued for the final study report. See Section 6.1.2 Post Marketing Requirements and Commitments.

Extrinsic Factors

The FDA does not agree with the Applicant's method of calculating combined molar Cmax for the drug interaction studies and is only reporting combined molar AUC.

- Effect of Other Drugs on Mobocertinib
    - Strong CYP3A Inhibitors: Mobocertinib is primarily metabolized by CYP3A. The FDA agrees that the Applicant's clinical data from Study 1006 demonstrated that coadministration of multiple doses of a strong CYP3A inhibitor, 200 mg itraconazole, significantly increased the PK of single 20 mg dose of mobocertinib and its active metabolites. The GMRs (90% CIs) for the combined molar AUC∞ of mobocertinib, AP32960, and AP32914 was 6.27 (5.20-7.56). Based on the single dose clinical data, physiologically based pharmacokinetic (PBPK) modeling was used to simulate the effect of strong CYP3A inhibitors on steady state exposure of mobocertinib and its active metabolites, which the FDA deemed adequate. Coadministration of multiple doses of itraconazole or ketoconazole (strong CYP3A inhibitors) was predicted to increase the steady state combined molar AUC of mobocertinib and its active metabolites by approximately 400%. As such, the FDA agrees with the Applicant's proposal for patients taking mobocertinib to avoid strong CYP3A inhibitors. See Appendix 18.3.3 - Physiologically based Pharmacokinetic Modeling Review.
    - Moderate CYP3A Inhibitors: The Applicant used PBPK modeling to simulate the effect of moderate CYP3A inhibitors (fluconazole, erythromycin, diltiazem, and verapamil) on steady state exposure of mobocertinib and its active metabolites, which the FDA deemed adequate. The FDA agrees with the Applicant's simulations showing that coadministration of multiple doses of moderate CYP3A inhibitors is predicted to increase steady state combined molar AUC of mobocertinib, AP32960, and AP32914 by approximately 120% to 200%. See Appendix 18.3.3 - Physiologically based Pharmacokinetic Modeling Review. The FDA agrees with the Applicant's proposal of a 50% reduction in the mobocertinib dose, with additional electrocardiogram monitoring, if the concomitant use of moderate CYP3A inhibitors cannot be avoided. See Section 6.3.2.4.

- Strong CYP3A inducers: The FDA agrees with the Applicant's clinical data from Study 1006 demonstrating that coadministration of multiple doses of a strong CYP3A inducer, 600 mg rifampin, significantly decreased the PK of a single 160 mg dose of mobocertinib and its active metabolites. The percent decrease of the combined molar AUC∞ of mobocertinib, AP32960, and AP32914 was 95%. The GMRs (90% CI) was 0.05 (0.04, 0.07). Based on the clinical data, PBPK modeling was used to simulate the effect of strong CYP3A inducers on steady state exposure of mobocertinib and its active metabolites, which FDA deemed adequate. Coadministration of multiple doses of rifampin (a strong CYP3A inducer) was predicted to decrease the steady state combined molar AUC of mobocertinib and its active metabolites by more than 90%. As such, FDA agrees with the Applicant's proposal to avoid strong CYP3A inducers. See Appendix 18.3.3 - Physiologically based Pharmacokinetic Modeling Review

- Moderate CYP3A inducers: The Applicant used PBPK modeling to simulate the effect of moderate CYP3A inducers on steady state exposure of mobocertinib and its active metabolites, which the FDA deemed adequate. The FDA agrees with the Applicant's simulations demonstrating that coadministration of multiple doses of efavirenz (a moderate CYP3A inducer) is predicted to decrease steady state combined molar AUC of mobocertinib, AP32960, and AP32914 by approximately 60%. See the PBPK review in Appendix 2.1. (b) (4) [redacted] .

- Inhibitors and Inducers of Other Transporters (OATP1B1, OATP1B3, P-gp, and BCRP): In vitro studies identified that mobocertinib was a substrate of P-gp and not a substrate of BCRP, OATP1B1, and OATP1B3. FDA agrees with the Applicant that there is low risk for a clinically meaningful effect of inhibitors or inducers of P-gp on the PK of mobocertinib because mobocertinib demonstrates high permeability and solubility in vitro. This is also consistent with the findings of the mass balance study, which suggested that 92% of mobocertinib is absorbed.

- Effect of Mobocertinib on Other Drugs

  - CYP3A Substrates – Mobocertinib, AP32960, and AP32914 are time-dependent inhibitors and inducers of CYP3A. The FDA agrees with the Applicant's results from the Study 1004, which suggests a 32% decrease in AUC of 3 mg oral midazolam (a sensitive CYP3A substrate) when coadministered with a single dose of 160 mg QD mobocertinib. Cmax of oral midazolam did not change. These data indicate that mobocertinib may reduce plasma concentrations and efficacy of coadministered medications that are predominantly metabolized by CYP3A. See Table 13. The FDA recommends

avoiding concomitant use of hormonal contraceptives and other CYP3A substrates, where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, the FDA recommends increasing the CYP3A substrate dosage in accordance with FDA-approved product labeling. See Section 6.3.2.4.

- CYP2B6, CYP2C8, and CYP2C9 substrates – The FDA agrees with the Applicant's in vitro studies that mobocertinib and its active metabolites do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations.

- P-gp Substrates – Mobocertinib is an in-vitro inhibitor of P-gp. The FDA agrees that PBPK modeling did not predict any clinically meaningful effect of multiple-dose administration of 160 mg QD mobocertinib on the PK of probe substrates (digoxin and dabigatran etexilate) for P-gp. See Appendix 18.3.3 Physiologically based Pharmacokinetic Modeling Review.

- BCRP Substrates – Mobocertinib is an in-vitro inhibitor of BCRP. (b) (4) [redacted] Whether the model can detect a positive DDI is unknown, and the in vitro to in vivo extrapolation of the Ki (inhibition constant) has not been established for the BCRP-mediated DDIs. As such, it is not known if mobocertinib and its active metabolites may increase BCRP substrate plasma concentrations in vivo, which may increase the incidence and severity of adverse reactions. See Appendix 18.3.3 Physiologically based Pharmacokinetic Modeling Review. As such, the FDA issued a PMR to address this safety concern. See Section 6.1.2 Post Marketing Requirements and Commitments.

- Substrates of Other Transporters (BSEP, MATE1, MATE2-K, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2): The FDA agrees with the Applicant's in vitro studies that mobocertinib and its active metabolites do not inhibit organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, or organic cation transporter (OCT) 2, multidrug and toxin extrusion protein (MATE) 1, MATE2-K, and OCT1 at clinically relevant concentrations

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Table 13: Summary of results of Study 1004 - Oral Midazolam 3 mg QD with or without single dose 160 mg QD mobocertinib

Study 1004 Objective	Pharmacokinetic parameter	LS Geometric Mean Ratio (90% CI) With/ Without
Oral Midazolam 3 mg QD **with or without single dose 160 mg QD mobocertinib**	Cmax (ng/mL)	1.03 (0.739, 1.420)
	AUCinf (h ng/mL)	0.676 (0.532, 0.859)

Source: EDR: CSR Study 1004 Table 15.2.5.1, 15.2.5.3, and 15.2.5.4 Received 16July2021. (EDR Submission 51 under NDA 215310)

6.2.2.3 Outstanding Issues

Data:

Not applicable

The Applicant's Position:

Three clinical pharmacology studies are currently ongoing at the time of this submission to assess the effect of severe renal impairment on the PK of mobocertinib (Study TAK-788-1007), the effect of moderate and severe hepatic impairment on the PK of mobocertinib (Study TAK-788-1008), and to characterize the effect of repeat-dose administration of mobocertinib on the PK of midazolam, a sensitive CYP3A substrate, in patients with NSCLC (Study TAK-788-1004).

The FDA's Assessment:

There are three clinical pharmacology PMRs. Two of the PMRs are to conduct and submit the final study reports for the ongoing hepatic and renal impairment studies. The third PMR is to assess the effect of mobocertinib and its active metabolites on the PK of a BCRP substrate. Based on the in vitro study, mobocertinib inhibits the BCRP transporter but the DDI simulations intended to evaluate the effect of mobocertinib on the PK of a BCRP substrate were inadequate because the BCRP substrate (sulfasalazine) model was evaluated by FDA to be inadequate.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:

Reference ID: 4857343

A summary of the mobocertinib drug product, the absorption, distribution, metabolism, and elimination properties of mobocertinib, drug-drug interaction potential, and the effect of mobocertinib on the QTc interval is provided below.

- **Drug Product**

One formulation of mobocertinib, an immediate release drug-in-capsule (DiC) oral formulation, differing in the manufacturing process used to prepare the drug substance (b) (4) was used during the clinical development of mobocertinib. The 3 drug substances are considered to be comparable on the basis of salt form, polymorphic form, purity profiles, and stability profiles. The particle size distribution for drug substance A and drug substance C are highly similar, and the specific surface area of drug substance C is bracketed by those of drug substance A and drug substance B.

Study TAK-788-1001 Part 3 compared the relative bioavailability of mobocertinib administered as drug-in-capsule by (b) (4) (DiC-B) versus drug-in-capsule by (b) (4) (DiC-A) in healthy subjects. The study results demonstrated that the geometric mean ratios of mobocertinib C_{max} and AUC_{∞}, as well as the geometric mean ratios for combined molar C_{max} and AUC_{∞} of mobocertinib, AP32960, and AP32914, were close to 1 when comparing 160 mg mobocertinib DiC-B to DiC-A. In addition, the 90% CIs were contained completely within the 80% to 125% equivalence limits, thereby supporting a conclusion of bioequivalence between DiC-B and DiC-A. Consequently, the results of this study indicate that the different manufacturing processes for drug substance A and B, particle size distribution, specific surface area, dose strength, and capsule size have no effect on oral absorption and systemic exposures of mobocertinib and its 2 active metabolites, AP32960 and AP32914.

Although no dedicated clinical relative bioavailability study comparing drug-in-capsule by (b) (4) (DiC-C) versus DiC-B or DiC-A has been conducted, this comparison has been assessed via population PK, model-based relative bioavailability, and PBPK analyses. Collectively, the results of these analyses support the conclusion that mobocertinib DiC-A, DiC-B, and DiC-C drug products are bioequivalent and therefore provide similar systemic exposures after single and multiple dose administration.

- **Metabolites**

Systemic exposures to the active metabolites AP32960 and AP32914 in terms of geometric mean molar AUC_{24} were 61.6% and 7.33% of mobocertinib AUC_{24}, respectively, in NSCLC patients receiving multiple-dose administration of 160 mg QD. AP32960 and AP32914 showed similar activity to mobocertinib in kinase and cellular assays.

- **Absorption**

After oral dosing of 160 mg QD, mobocertinib is absorbed with a median t_{max} of approximately 4 hours postdose. The median t_{max} values for AP32960 and AP32914 were also 4 hours postdose. The plasma AUC_{24} of mobocertinib and the combined molar AUC_{24} of mobocertinib, AP32960, and AP32914, after single-dose and multiple-dose administration increased approximately dose proportionally over the 5 to 180 mg dose range based on the noncompartmental analyses in

patients with NSCLC (Study AP32788-15-101) and over the 40 to 160 mg single-dose range based on the noncompartmental analyses in healthy subjects (Study TAK-788-1001). The absolute bioavailability of mobocertinib was determined to be 36.7% in Study TAK-788-1002 Period 1. The fraction absorbed for mobocertinib is estimated to be approximately 91.7% based on the results from the human ADME study (Study TAK-788-1002 Period 2).

- **Distribution**

The geometric mean apparent volume of distribution at steady state for mobocertinib is estimated to be 3510 L based on the population PK model. Based on in vitro data, mobocertinib, AP32960, and AP32914 are 99.3%, 99.5%, and 98.6% bound to human plasma proteins, respectively. Data from the human ADME study (Study TAK-788-1002 Period 2) demonstrated that mobocertinib, AP32960, and AP32914 did not show preferential distribution into human whole blood over plasma. The geometric mean blood-to-plasma ratio based on combined molar mobocertinib, AP32960, and AP32914 AUC_{∞} was 0.884.

- **Metabolism**

Metabolism appears to be the major mechanism of mobocertinib clearance. Using recombinant human cytochrome P450 enzymes (rhCYPs), the percent contribution of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 to mobocertinib metabolism was 0.3%, 1.1%, 2.4%, 1.9%, 0.1%, 0.6%, and 93.5%, respectively. Mobocertinib was extensively metabolized by rhCYP3A4/5 with AP32960 as the predominant metabolite (>20%) and AP32914 as a minor metabolite (approximately 1%). AP32960 and AP32914 were metabolized almost exclusively by CYP3A4/5.

- **Elimination**

The geometric mean effective half-life for mobocertinib is 17.6 h based on the population PK analysis. After repeat dosing in patients with NSCLC, moderate accumulation of mobocertinib systemic exposure was observed at doses ≤120 mg QD. However, administration of mobocertinib 160 mg QD resulted in similar Cycle 1 Day 1 and Cycle 2 Day 1 mobocertinib AUC_{24} with a geometric mean accumulation ratio of 1.03. Negligible accumulation of mobocertinib exposure at 160 mg QD along with less than dose-proportional increases in mobocertinib exposure from 120 to 160 mg QD suggest autoinduction of the apparent oral clearance of mobocertinib likely via induction of CYP3A.

The apparent oral clearance of mobocertinib is 108 L/h based on the results of the population PK analysis. In the human ADME study (Study TAK-788-1002 Period 2), 76.0% of the administered radioactive dose was recovered in the feces and 3.57% of the dose was recovered in the urine. Only 1.13% of the administered mobocertinib dose was recovered in the urine as unchanged mobocertinib, AP32960, and AP32914 combined, thereby suggesting that renal excretion is not a major pathway of elimination for mobocertinib. Taken together, these results support that renal clearance does not meaningfully contribute to overall mobocertinib clearance and are consistent with metabolism being the major clearance mechanism.

- **Effect of Other Drugs on Mobocertinib**

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The results of in vitro studies indicate that mobocertinib, AP32960, and AP32914 are predominantly metabolized by CYP3A.

When mobocertinib was coadministered with itraconazole (Study TAK-788-1006 Part 1), the combined molar C_{max} and AUC_{∞} of mobocertinib, AP32960, and AP32914 were approximately 186% and 527% higher, respectively, in the presence of itraconazole than when mobocertinib was administered alone. In the PBPK analyses, after multiple-dose administration of 160 mg QD mobocertinib, the model-predicted geometric mean steady-state AUC ratios for combined molar exposure of mobocertinib, AP32960, and AP32914 with versus without coadministration of strong, moderate, or weak CYP3A inhibitors were approximately 5 (itraconazole, 5.19; ketoconazole, 4.74), approximately 2 (fluconazole, 2.35; erythromycin, 2.16), and 1.16 (cimetidine), respectively.

In the clinical Study TAK-788-1006 Part 2, the combined molar C_{max} and AUC_{∞} of mobocertinib, AP32960, and AP32914 were reduced in the presence of rifampin by approximately 92% and 95%, respectively, corresponding least-squares geometric mean ratios (90% CI) of 0.08 (0.07, 0.11) and 0.05 (0.04, 0.07), respectively. In the PBPK analyses, after multiple-dose administration of 160 mg QD mobocertinib, the model predicted that the strong CYP3A inducer rifampin may reduce the steady-state combined molar AUC of mobocertinib, AP32960, and AP32914 by >90% (geometric mean ratio of 0.08). An approximately 60% decrease (geometric mean AUC ratio of 0.42) in steady state combined molar AUC of mobocertinib, AP32960, and AP32914 was predicted in the presence of the moderate CYP3A inducer, efavirenz.

- **Effect of Mobocertinib on Other Drugs**

In vitro studies indicate that mobocertinib, AP32960, and AP32914 are reversible inhibitors of CYP2B6, CYP2C8, and CYP3A. In addition, mobocertinib, AP32960, and AP32914 were mechanism-based inhibitors of CYP3A in vitro. In human hepatocytes, mobocertinib, AP32960, and AP32914 were potent inducers of CYP3A.

In the PBPK analyses, no clinically meaningful DDIs were predicted following coadministration of multiple doses of 160 mg QD mobocertinib with probe substrates of CYP2B6, CYP2C8, and CYP2C9 as coadministration of mobocertinib resulted in a less than 15% change in the AUC of the probe substrate for each CYP isozyme. Therefore, administration of mobocertinib is not expected to result in clinically meaningful inhibition of CYP2B6, CYP2C8, and CYP2C9 in vivo. For the CYP3A probe substrates, alprazolam and midazolam, the PBPK analyses predicted geometric mean AUC and C_{max} ratios with versus without mobocertinib coadministration of 0.82 and 0.98 for alprazolam, and 0.63 and 0.70 for midazolam, respectively. Therefore, the PBPK analyses predicted a net weak induction effect on CYP3A activity in vivo following mobocertinib administration.

The ongoing clinical Study TAK-788-1004 is evaluating the effect of multiple-dose 160 mg QD mobocertinib administration on the PK of orally and intravenously administered midazolam, a sensitive CYP3A substrate.

- **Transporter-Based Interactions**

Mobocertinib is an in vitro inhibitor of P-gp and BCRP. However, the PBPK model predicted no clinically meaningful effect of multiple-dose administration of 160 mg QD mobocertinib on the PK of probe substrates for P-gp or BCRP.

Mobocertinib is not an in vitro inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. Although mobocertinib inhibited MATE1, MATE2-K, and OCT1 in vitro, the potential for in vivo inhibition of these transporters is inferred to be low.

Mobocertinib is not a substrate of OATP1B1 or OATP1B3. Mobocertinib, AP32960, and AP32914 were in vitro substrates for P-gp. Mobocertinib and AP32914 were not BCRP substrates in vitro; however, AP32960 may be a weak BCRP substrate. Given that mobocertinib exhibits high solubility and high permeability in vitro, P-gp inhibitors are unlikely to increase plasma concentrations of mobocertinib.

- **Effect of Mobocertinib on QTc**

Estimated weighted sum of mobocertinib, AP32960, and AP32914 plasma concentration was a statistically significant predictor of QTcF and JT_{peak}. The model-based prediction of QTcF interval change from baseline at the steady-state C_{max} following 160 mg QD mobocertinib was 12.7 msec (90% CI: 8.69, 16.8). The corresponding prediction for the JT_{peak} interval change from baseline was 11.1 msec (90% CI: 3.12, 18.9). No statistically significant relationship was identified between concentration and the RR interval, supporting the lack of a clinically meaningful effect on heart rate.

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

The clinical pharmacology of mobocertinib and its 2 active metabolites, AP32960 and AP32914, has been comprehensively evaluated via in vitro studies, dedicated clinical studies, and integrated model-based analyses using data from across the clinical development program.

<u>The FDA's Assessment:</u>

The FDA agrees with the Applicant that the PK of mobocertinib and its two active metabolites, AP32960 and AP32914, were adequately characterized except for the following:

- The PBPK model used to predict the effect of multiple-dose administration of 160 mg QD mobocertinib on the PK of probe substrates for BCRP is inadequate because the BCRP substrate (sulfasalazine) model used as part of the simulations is inadequate. The sulfasalazine model was developed using results from a pharmacogenetic study to quantify the contribution of BCRP to its disposition. Whether the model can detect a positive DDI is unknown, and the in vitro to in vivo extrapolation on the Ki (inhibition constant) has not been established for the BCRP-mediated DDIs. As such, it is not known if mobocertinib and its active metabolites may increase BCRP substrate plasma concentrations in vivo, which may increase the incidence and severity of adverse reactions. See Appendix 18.3.3 - Physiologically-based Pharmacokinetic Modeling Review. Therefore, FDA issued a PMR to address this safety concern. See Section 6.1.2 - Post Marketing Requirements and Commitments.

- The FDA does not agree with the Applicant's concentration-QTc analysis method because the effect of time on the QTc interval cannot be estimated with confidence in the absence of a placebo control. The FDA reviewer's analysis suggested that mobocertinib treatment is associated with a concentration dependent QTc prolongation effect. At therapeutic doses (160 mg QD) of mobocertinib, mean increases in the QTc interval of 23 msec (UCL: 26 msec) were detected in this QT assessment by the FDA. For additional details, see the Interdisciplinary Review Team for Cardiac Safety Studies: QT Study Review

Of note, three capsule formulations were used in the clinical pharmacology studies (DiC-A, DiC-B, and DiC-C). The dose finding and confirmation portions of the study (Parts 1 and 2 of Study 101) were conducted with DiC-A and -B. Additionally, the low-fat food effect study (Study 1001 Part 2) and the DDI study with a strong CYP3A inhibitor (Study 1006 Part 1) used formulation DiC-A. The ongoing hepatic impairment study (Study 1008) is using formulation DiC-B. The Applicant conducted a relative bioavailability study to bridge between DiC-A and DiC-B (Study 1001 Part 3), which the FDA deemed adequate. See Table 14.

The to-be-marketed formulation is DiC-C. The extension study from which the majority of the primary efficacy population is derived (Study 101 Part 3) used DiC-C, as did the mass balance and absolute bioavailability study (Study 1002), high fat food effect study (Study 1005), and the DDI study with a strong CYP3A inducer (Study 1006 Part 2). The ongoing studies for renal impairment (Study 1007) and DDI study between TAK-788 and a sensitive CYP3A substrate (Study 1004) are also using DiC-C. Additional PK comparability between DiC-A and DiC-C was confirmed by pooled PK analysis comparing 10 fasted healthy subjects treated with single dose of 160 mg using the DiC-A formulation from Study 1001 Part 2 to 13 fasted healthy subjects treated with a single dose of 160 mg using the DiC-C formulation from Study 1005. See the Biopharmaceutics review and Figure 7 below.

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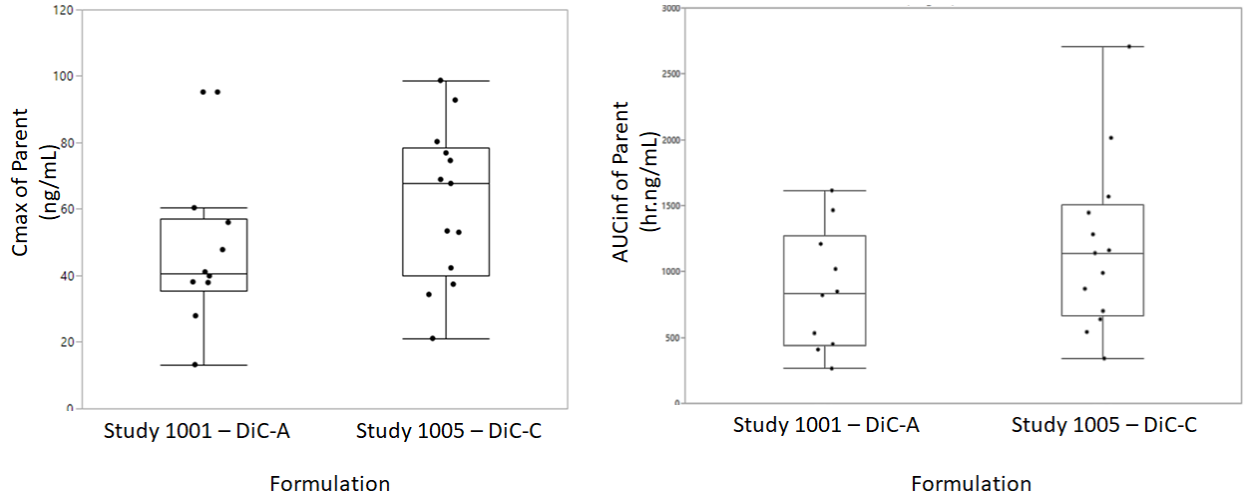
Table 14: Summary of findings from Study 1001 Part 3 - Relative bioavailability of mobocertinib DiC-B compared to DiC-A under fasted conditions

Study 1001 part 3 Objective	Pharmacokinetic parameter	LS Geometric Mean Ratio (90% CI) DiC-B / DiC-A
Relative Bioavailability of mobocertinib DiC-B compared to DiC-A	Combined Molar Cmax (ng/mL)	0.930 (0.870, 0.995)
	Combined Molar AUC_{inf} (h.ng/mL)	0.947 (0.886, 1.01)

Source: EDR Study 1001 Part 3 CSR Table 11.o

Figure 7: Summary of findings from pooled PK analysis comparing the exposure of a single 160 mg QD dose of mobocertinib formulation DiC-A to DiC-C



Source: Reviewer analysis from EDR Studies 1001 and 1005 data sets; 10 healthy subjects fasted treated with single dose of 160 mg using the DiC-A formulation from Study 1001 Part 2 and 13 healthy subjects fasted treated with a single dose of 160 mg using the DiC-C formulation from Study 1005.

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6.3.2 Clinical Pharmacology Questions

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

Data:

Data from the Pooled Prior Platinum Analysis Set of Study AP32788-15-101 demonstrated that a mobocertinib dose of 160 mg QD was effective at achieving durable confirmed objective responses. Additional details regarding the efficacy of mobocertinib in Study AP32788-15-101 are provided in Section 8.1.2. Results from the Pooled Prior Platinum Analysis Set 01 November 2020 data cutoff are presented Section 8.1.2.1.

Exposure-response analyses were conducted based on the reported efficacy data from patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations enrolled in Parts 1, 2, or 3 of Study AP32788-15-101, who were treated with 160 mg QD mobocertinib and had received prior platinum-based chemotherapy (i.e., the Pooled Prior Platinum Analysis Set). In the exposure-efficacy analyses, no statistically significant relationship was identified between combined molar exposure of mobocertinib, AP32960, and AP32914, and clinical response. This indicates that the efficacy benefit of mobocertinib was consistent across the observed range of exposures achieved after administration of 160 mg QD mobocertinib.

The Applicant's Position:

Yes, the clinical pharmacology program provides supportive evidence of the effectiveness of 160 mg QD mobocertinib for the treatment of patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations as demonstrated in Study AP32788-15-101. Specifically, the results of the exposure-efficacy analyses indicate that the efficacy benefit of mobocertinib was consistent across the range of exposures achieved after administration of 160 mg QD.

The FDA's Assessment:

The FDA agrees that the clinical pharmacology program provides evidence of effectiveness for the proposed dosage of 160 mg QD. In short, 160 mg QD demonstrated a numerically higher ORR than all other doses tested, which is supported by a relatively flat but positive exposure response relationship for efficacy. See Section 6.2.2.1 General Dosing for additional details.

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

Data:

Mobocertinib at a dose of 160 mg QD presents a manageable safety profile typical of next generation EGFR TKIs, and treatment-emergent adverse events were clinically manageable. A total of 75% of patients in the Pooled Prior Platinum Analysis Set were able to continue treatment at the starting dose of 160 mg mobocertinib without a dose reduction due to an adverse event. Additional details regarding the safety of mobocertinib are provided in Section 8.2.

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In the exposure-safety analyses for the Pooled Prior Platinum Analysis Set, no statistically significant relationship was identified between combined molar exposure of mobocertinib, AP32960, and AP32914 and the occurrence of treatment-emergent diarrhea, nausea, paronychia, rash, stomatitis, and vomiting. However, a decrease in systemic exposure corresponding to a dose reduction from 160 mg to 120 mg QD resulted in odds ratios for each adverse event that were less than 1, indicating trends toward lower probability of adverse events with lower exposure. In addition, no statistically significant relationship was identified between systemic exposures and the time to the first dose reduction.

As described in Section 6.3.2.1, the exposure-efficacy analysis results indicated a consistent efficacy benefit across the range of exposures achieved after administration of 160 mg QD mobocertinib.

The Applicant's Position:

Taken together, the exposure-efficacy and exposure-safety analysis results support a favorable benefit/risk profile of the 160 mg QD mobocertinib dosing regimen for the general patient population for the proposed indication.

The FDA's Assessment:

The FDA agrees that the proposed dosage of 160 mg QD is adequately justified for the proposed patient population by the data and analyses included in the NDA. The dosage of 160 mg QD demonstrated a numerically higher ORR than all other doses tested, which is supported by a relatively flat but positive exposure response relationship for efficacy. Of note, 160 mg QD is the MTD.

Additionally, the dose intensity and clinical experience of dose reductions and discontinuations suggested that 160 mg QD was generally well tolerated in both the efficacy (n=114) and safety (n=256) populations; and the positive trend for the exposure response relationship for safety supported adequate management of adverse events by dose reduction from 160 mg to 120 mg, then to 80 mg QD. Please see Section 6.2.2.1 General Dosing for additional details.

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

Data:

Data related to the effect of intrinsic factors on the PK of mobocertinib and its active metabolites are presented in Section 6.2.2.2.

The Applicant's Position:

The population PK analysis demonstrated that age, sex, body weight, race, mild or moderate renal impairment (ie, creatinine clearance ≥30 mL/min; estimated glomerular filtration rate ≥30 mL/min/1.73 m^2), and mild hepatic impairment (ie, total bilirubin ≤ULN and AST or ALT >ULN or total bilirubin >1-1.5 times ULN and any AST or ALT) do not affect the PK of

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mobocertinib and its active metabolites. Therefore, no alternative dosing regimen or management strategy is required for these intrinsic patient factors.

The effect of severe renal impairment on mobocertinib PK is being evaluated in the ongoing Study TAK-788-1007, and the effect of moderate and severe hepatic impairment on mobocertinib PK is being evaluated in the ongoing Study TAK-788-1008.

The FDA's Assessment:

The FDA agrees with the Applicant that no alternative dosing strategies are needed based on age (18-86 yrs.), sex (183 male, 244 female), race (283 White, 19 Black, 115 Asian), or body weight (37-132 kg), mild or moderate renal impairment (178 mild, 30 moderate) and mild hepatic impairment (54 mild). See Clinical PMC 1 regarding collection of additional clinical safety and efficacy data in patients of race/ethnicity that are underrepresented in the data submitted to the NDA.

The effect of moderate and severe hepatic impairment on the PK of mobocertinib and its active metabolites is being evaluated in the ongoing Study 1008. The effect of severe renal impairment on the PK of mobocertinib and its active metabolites is being evaluated in the ongoing Study 1007. For moderate hepatic impairment, FDA used topline results submitted from Study 1008 during the review period to support the recommendation that no dose adjustments are necessary for patients with moderate hepatic impairment. Data from patients with severe hepatic impairment or severe renal impairment were not available in the current submission and a recommended dosage has not been established for patients with severe hepatic impairment or severe renal impairment. See Section 6.2.2.2 - Therapeutic Individualization for additional details.

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

Data:

Data related to the effect of food on the PK of mobocertinib and its active metabolites is presented in Section 6.2.2.1. Data related to potential drug-drug interactions are presented in Section 6.2.2.2.

The Applicant's Position:

A low-fat meal or high-fat meal had no clinically meaningful effect on the combined molar exposure (C_{max} and AUC_{∞}) of mobocertinib, AP32960, and AP32914, as the 90% CIs for the geometric mean ratios for C_{max} and AUC_{∞} were contained completely within the 80% to 125% equivalence limits. Therefore, mobocertinib may be taken with or without food.

There are clinically relevant drug-drug interactions for mobocertinib. The proposed management strategies are presented below:

Clinical study results and PBPK analyses demonstrated that strong and moderate CYP3A inhibitors increase combined molar exposures of mobocertinib, AP32960, and AP32914. Therefore, the concomitant use of strong and moderate CYP3A inhibitors with mobocertinib should be avoided. If the concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of mobocertinib should be reduced by approximately 50% (eg, from 160 mg to 80 mg, 120 mg to 40 mg, or 80 mg to 40 mg, based on the available capsule strengths). No dose adjustment is needed when mobocertinib is coadministered with weak CYP3A inhibitors.

Strong and moderate CYP3A inducers decrease combined molar exposures of mobocertinib, AP32960, and AP32914 based on the results of a clinical study and PBPK analyses. Thus, the concomitant use of strong and moderate CYP3A inducers with mobocertinib should be avoided. If the concomitant use of moderate CYP3A inducers cannot be avoided, the dose of mobocertinib should be gradually increased in 40 mg increments after 7 days of treatment with mobocertinib and the moderate CYP3A inducer, as tolerated, up to a maximum of twice the mobocertinib dose that was tolerated prior to the initiation of the moderate CYP3A inducer.

The PBPK analyses predicted a net weak induction effect on CYP3A activity following mobocertinib administration, which is consistent with the autoinduction observed with the 160 mg QD mobocertinib dose in Study AP32788-15-101. As a result, mobocertinib may reduce plasma concentrations of coadministered medications that are predominantly metabolized by CYP3A. The concomitant use of mobocertinib with CYP3A substrates can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates. Mobocertinib may also induce other enzymes and transporters (eg, CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (eg, pregnane X receptor activation).

The FDA's Assessment:

Moderate CYP3A inhibitors: The FDA agrees with the Applicant's proposal to reduce the dosage of mobocertinib by 50% from 160 mg QD to 80 mg QD when coadministration of

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moderate CYP3A inhibitors cannot be avoided. However, the FDA further recommends that the dose reduction is accompanied by enhanced ECG monitoring for the following reasons:

- The observed positive exposure-response relationships for safety, in particular, QTc interval prolongation. See Section 6.2.2 and the Interdisciplinary Review Team for Cardiac Safety Studies: QT Study Review

- The estimated total combined molar exposure increase of mobocertinib and its active metabolites ranged from 30%-80% compared to the 160 mg QD alone. See Appendix 18.3.3 Physiologically based Pharmacokinetic Modeling Review

- It is not known if further dose reductions beyond 80 mg to 40 mg may reduce efficacy. See section 6.2.2 General Dosing and Therapeutic Individualization

Moderate CYP3A Inducers: FDA does not agree with the Applicant's proposal (b) (4) Mobocertinib is an auto inducer of its own metabolism by CYP3A. The PBPK model used for the Applicant's simulations is a fit-for-purpose model, i.e., clinical data at doses of up to180 mg were used for model adjustment. The model has not been validated for doses higher than 180 mg, where PK nonlinearity is likely due to mobocertinib autoinduction of CYP3A. As such, the induction effect at doses higher than 180 mg is unknown. Additionally, there is no clinical data to confirm mobocertinib dose linearity above 180 mg QD. As such, the resultant exposure from administration of doses above 180 mg could lead to different than expected exposures. Given the known exposure-response relationships, this unpredictable change in mobocertinib exposure might lead to a safety concern (higher exposure) or efficacy concern (lower exposure). Lastly, the estimated total combined molar exposure of mobocertinib and its active metabolites was predicted to decrease by more than 50%, (b) (4) The FDA recommends avoiding coadministration of moderate CYP3A inducers with mobocertinib. See Section 6.2.2.2 Therapeutic Individualization.

CYP3A Substrates – FDA added labeling recommendations to avoid concomitant use of hormonal contraceptives and other CYP3A substrates, where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, the FDA added labeling recommendations to increase the CYP3A substrate dosage in accordance with the FDA approved product package insert. Mobocertinib, AP32960, and AP32914 are time-dependent inhibitors and inducers of CYP3A and results from the clinical Study 1004 suggest mobocertinib may reduce plasma concentrations and efficacy of coadministered medications that are predominantly metabolized by CYP3A. See Section 6.2.2.2 - Therapeutic Individualization.

X	X
Kimberly Maxfield	Jeanne Fourie Zirkelbach
Primary Reviewer	Team Leader

7.0 SOURCES OF CLINICAL DATA

7.1 Table of Clinical Studies

The Applicant's Position:

The clinical studies comprising this application are summarized in Table 15.

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Table 15: Mobocertinib Clinical Studies Relevant to the Efficacy, Safety, and Clinical Pharmacology Evaluation

Protocol No. and Status	Primary Study Objective(s)	Study Design and Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Patients)
Efficacy and safety studies				
AP32788-15-101 [a]				
Part 1 (dose-escalation) Status: Ongoing (primary analysis is complete)	Safety, PK profile, and RP2D	Open-label, multicenter, dose-escalation study (3 + 3 design with additional expansion) in patients with advanced NSCLC who are refractory to standard available therapies.	Total daily doses explored include 5, 10, 20, 40, 80, 120, 160, and 180 mg orally, continuously in 28-day cycles.	N = 73
Part 2 (expansion phase) Status: Ongoing (primary analysis is complete)	Anti-tumor activity	Open-label, multicenter study with 7 histologically and molecularly defined cohorts of patients with advanced NSCLC or other solid tumors with *EGFR* or *HER2* mutations.	160 mg QD orally, continuously in 28-day cycles.	Total: N= 136
Part 3 (pivotal extension phase) Status: Ongoing (primary analysis is complete)	Efficacy (confirmed ORR, per IRC)	Open-label, multicenter study with single-arm extension cohort of patients with locally advanced or metastatic NSCLC harboring *EGFR Exon 20* insertion mutations who have received at least 1 prior line of therapy for locally advanced or metastatic NSCLC.	160 mg QD orally, continuously in 28-day cycles.	N = 96

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Table 15: Mobocertinib Clinical Studies Relevant to the Efficacy, Safety, and Clinical Pharmacology Evaluation

Protocol No. and Status	Primary Study Objective(s)	Study Design and Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Patients)
TAK-788-1003 Status: Ongoing (non-IND study; primary analysis of Part 1 is complete)	Part 1: Safety, tolerability (DLTs/ RP2D)	Part 1: Open-label, multicenter, dose-escalation study in Japanese patients with locally advanced or metastatic NSCLC.	Part 1: 40 mg to 160 mg QD orally, continuously in 28-day cycles.	N = 20 in Part 1
TAK-788-5002 Status: Complete	Anti-tumor effectiveness of currently used standard of care (rwORR, rwDOR).	Retrospective observational study of patients with NSCLC with *EGFR Exon 20* insertion mutations: real-world data generation of natural history.	NA	NA
Clinical pharmacology studies				
TAK-788-1001 Status: Complete	Part 1: Safety and tolerability. Part 2: Characterize low-fat meal effect on PK. Part 3: Relative bioavailability (b) (4) capsule and (b) (4) capsule.	Randomized, double-blind, placebo-controlled, single rising dose study (Part 1) followed by a crossover evaluation of the low-fat food effect on the PK of mobocertinib (Part 2) followed by a relative bioavailability study of mobocertinib capsules (Part 3) in healthy subjects.	Part 1: 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg orally, single dose. Part 2: 120 mg and 160 mg orally, 2 single doses under fed (low-fat meal) and fasted conditions separated by 7-day washout. Part 3: 160 mg orally, 2 single doses separated by 7-day washout.	N = 69 (mobocertinib N= 59; placebo N = 10)

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Table 15: Mobocertinib Clinical Studies Relevant to the Efficacy, Safety, and Clinical Pharmacology Evaluation

Protocol No. and Status	Primary Study Objective(s)	Study Design and Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Patients)
TAK-788-1002 Status: Complete	Period 1: Absolute bioavailability microdose IV and oral administration. Period 2: Absorption, distribution, metabolism, and excretion.	Open-label, single-dose, 2-period study Period 1: A total of 6 healthy subjects received a single oral dose of mobocertinib and a microdose of [^{14}C]- mobocertinib IV injection Period 2: The 6 healthy subjects from Period 1 received a single oral solution dose of [^{14}C]-mobocertinib.	Period 1: 160 mg capsule orally and 50 µg [^{14}C]- mobocertinib IV, single doses separated by 3.75 hours. Period 2: 160 mg [^{14}C]- mobocertinib orally, single dose. There was a 9-day washout between Periods 1 and 2.	N = 7
TAK-788-1005 Status: Complete	Characterize high-fat meal effect on PK.	2-period, randomized, crossover study of fed versus fasting in healthy subjects.	160 mg orally, 2 single doses under fed (high-fat meal) and fasted conditions separated by 10-day washout.	N = 14
TAK-788-1006 Status: Complete	Drug-drug interaction study of strong CYP3A inhibitor (Part 1) and CYP3A inducer (Part 2) on the PK of mobocertinib.	Single-sequence, 2-period study with single dose of mobocertinib in healthy subjects.	Part 1: 20 mg mobocertinib, 2 single doses. 200 mg itraconazole solution QD, 14 doses. Part 2: 160 mg mobocertinib, 2 single doses. 600 mg rifampin QD, 13 doses.	N = 24

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Table 15: Mobocertinib Clinical Studies Relevant to the Efficacy, Safety, and Clinical Pharmacology Evaluation

Protocol No. and Status	Primary Study Objective(s)	Study Design and Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Patients)

CYP: cytochrome P-450; DLT: dose-limiting toxicity; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; IND: Investigational New Drug; IRC: independent review committee; IV: intravenous; NA: not applicable; NDA: New Drug Application; NSCLC: non-small cell lung cancer; ORR: objective response rate; PK: pharmacokinetic(s); QD: once daily; RP2D: recommended Phase 2 dose; rwDOR: real-world duration of response; rwORR: real-world objective response rate.

[a] In addition to the analysis of each part individually, efficacy analyses were conducted on the following:

- Pooled Prior Platinum Analysis Set (N = 114) 29 May 2020 data cutoff and 01 November 2020 data cutoff: patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations who had previously been treated with platinum-based chemotherapy from Part 1 (treated at the recommended dose), Expansion Cohort 1 of Part 2, and Part 3.
- Expanded Refractory Exon 20 Cohort (N = 28) 29 May 2020 data cutoff: patients with previously treated NSCLC with *EGFR Exon 20* insertion mutations treated with 160 mg QD in Part 1 and Expansion Cohort 1 of Part 2.
- Each part was analyzed individually using the 29 May 2020 data cutoff.

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The FDA's Assessment:

The FDA agrees with the Applicant's description of the clinical studies included in this application.

8.0 STATISTICAL AND CLINICAL EVALUATION

8.1 Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Position:

The primary efficacy analysis in the submission is from the Pooled Prior Platinum Analysis Set from Study AP32788-15-101 (referred to as Study 101), as was agreed between the Agency and Applicant at the Pre-NDA meeting on 10 November 2020.

Study 101 was a global, Phase 1/2, pivotal, single-arm, open-label, 3-part study. This study included a dose-escalation phase (Part 1), which established the recommended Phase 2 dose (RP2D) of mobocertinib, followed by an expansion phase in 7 distinct disease cohorts treated at the RP2D (Part 2), and an extension cohort (Part 3). The extension cohort (Part 3) of Study 101 included patients with locally advanced or metastatic disease, who were treated at the recommended dose of 160 mg once daily (QD), and who had been previously treated with at least 1 prior line of therapy (97 enrolled, 96 treated).

Thus, the primary efficacy analysis is:

- The Pooled Prior Platinum Analysis Set (N = 114) included patients from all parts of Study 101 with metastatic NSCLC with *EGFR Exon 20* insertion mutations who had previously been treated with platinum-based chemotherapy. Patients in the Pooled Prior Platinum Analysis Set were administered the recommended dose of 160 mg QD (Part 1 [n = 6]; Expansion Cohort 1 of Part 2 [n = 22]; and Part 3 [n = 86]) (Section 8.1.2.1).

Supportive efficacy evidence included in the submission are:

- Results from Part 3 (extension cohort) of Study 101, 29 May 2020 data cutoff;
- Results from Parts 1 and 2 (dose-escalation and expansion cohorts) of Study 101, 29 May 2020 data cutoff;
- Historical benchmark data from an analysis of real-world data (RWD) from study TAK-788-5002 and other relevant RWD sources (Section 8.1.2.2).

Safety data are provided from Study 101, Part 1 of Study TAK-788-1003, and several clinical pharmacology studies, as well as an integrated analysis of safety in 325 patients treated with mobocertinib from the 29 May 2020 data cutoff (Section 8.2).

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8.1.1 Design

8.1.1.1 AP32788-15-101 (Study 101)

The Applicant's Position:

Study 101 was a Phase 1/2, pivotal, single-arm, open-label, multicenter clinical trial in 3 parts. Study 101 is summarized in Table 16. The Pooled Prior Platinum Analysis Set will serve as the primary efficacy analysis population. The results for the Pooled Prior Platinum Analysis Set are presented in Section 8.1.2.1.

Table 16: Overview of Study 101

Alternative names for Study	AP32788-15-101
Title	A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer
NCT	NCT02716116
Design and description	Phase 1/2, pivotal, single-arm, open-label, multicenter clinical trial in 3 parts This is an open-label, multicenter, single-agent, single-arm, continuously conducted Phase 1/2 study. This study started as a first-in-human dose-escalation study (Part 1), which included an expansion phase in distinct disease cohorts (Part 2) and advanced to a Phase 3 global extension cohort to further explore the safety, activity, and clinical benefit of mobocertinib in patients with previously treated NSCLC whose tumor harbored an *EGFR Exon 20* insertion mutation (Part 3). • Part 1 employed sequential dose escalation of oral mobocertinib using a standard 3+3 design, starting at 5 mg administered orally QD, and increasing in increments until the MTD was identified. Part 1 assessed safety, PK profile, and RP2D of orally administered mobocertinib in these patients; • Part 2 (expansion cohorts) included 7 additional histologically and molecularly defined cohorts, with Expansion Cohort 3 being limited to patients with active, measurable CNS metastases. The dose and schedule for Part 2 were determined based on the RP2D and schedule determined in Part 1 (dose-escalation) (ie, 160 mg QD); • Part 3 (extension cohort) was an international, multicenter, open-label cohort and was designed to evaluate the efficacy of mobocertinib at 160 mg QD in patients with locally advanced or metastatic NSCLC whose tumors harbored *EGFR Exon 20* insertion mutations and who had been previously treated. All patients in Part 3 were to have an *EGFR Exon 20* insertion mutation. Subjects who participated in Part 1, 2, or 3, received mobocertinib 160 mg QD, and who were previously treated with platinum-based chemotherapy were included in the Pooled Prior Platinum Analysis Set.
Primary objective and patient population	• Part 1 and Part 2: o To determine the safety profile of orally administered mobocertinib; o To identify the recommended Phase 2 dose (RP2D), DLTs, and the

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Table 16: Overview of Study 101

Alternative names for Study	AP32788-15-101
	maximum tolerated dose (MTD) of mobocertinib; o To determine the pharmacokinetic (PK) profile of mobocertinib and its active metabolites, AP32960 and AP32914; o To evaluate the anti-tumor activity of mobocertinib in NSCLC with *EGFR* or *HER2* mutations; o To explore relationships between tumor and/or plasma biomarkers and mobocertinib efficacy, safety, and/or cytochrome P-450 (CYP)3A induction; o To evaluate the anti-tumor activity of mobocertinib in patients with solid tumors other than NSCLC with *EGFR* or *HER2* mutations. • Part 3: To determine the efficacy of mobocertinib, as evidenced by confirmed objective response rate (cORR), as assessed by the IRC, in patients with locally advanced or metastatic NSCLC harboring EGFR in-frame exon 20 insertion mutations and who had received at least 1 prior line of therapy for locally advanced or metastatic NSCLC.
Primary endpoint	• Part 1: RP2D of orally administered mobocertinib; • Part 2: Investigator-assessed cORR (using RECIST v1.1), except for Expansion Cohort 3, in which iORR (as assessed by the IRC) was the primary endpoint, and Expansion Cohort 6, in which cORR (as assessed by the IRC, using RECIST v1.1) was the primary endpoint; • Part 3: cORR, as assessed by the IRC, per RECIST v1.1.
Treatments	• Part 1: 5, 10, 20, 40, 80, 120, 180 mg QD; 40, 60, 160 mg BID; • Part 2: 160 mg QD; • Part 3: 160 mg QD.
Sample size	• Part 1 and Part 2: Sample size was determined based on clinical rather than statistical considerations. The number of patients in this study was consistent with Phase 1 dose finding studies; With this design, the estimate of the rate of DLT at the MTD was in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which was 1 step above the MTD, was 0.33. • Part 3: o n=91; o Sample size was determined so that it would allow us to state that the true ORR was greater than threshold response rate of 20%. Approximately 91 patients with NSCLC with tumors harboring *EGFR Exon 20* insertion mutations on the basis of a local test would be enrolled to include approximately 73 patients with centrally confirmed *EGFR Exon 20* insertion mutations, assuming a 20% discrepancy between the documented mutation status by local testing results and central testing using an analytically validated central test. Assuming a true response rate of 36% in patients with locally documented *EGFR Exon 20* insertion mutations, 91 patients would allow the study to have over 91% power to rule out an uninteresting rate of 20% in this population

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Table 16: Overview of Study 101

Alternative names for Study	AP32788-15-101
	with a 1-sided alpha of 0.025.
Investigational sites	Part 1 and Part 2: (dose-escalation and expansion cohorts) were conducted at 28 study sites in the U.S.; and Part 3 (extension cohort) was conducted at 70 study centers in the following regions: 30 sites in North America (U.S.), 19 sites in Europe (Germany, Spain, Great Britain, Italy), and 21 sites in Asia (China, Japan, South Korea, Taiwan).
Study period	First patient dosed: 16 June 2016 Last patient first dose: 29 March 2019
Data cutoff dates	Primary analysis: 29 May 2020 Follow-up analysis: 01 November 2020
Study status	The study is currently ongoing, with the end of study planned for 3 years after enrollment of the last patient, unless stopped earlier due to futility or Applicant decision. Of the 96 subjects in Part 3, 38 (39.6%) were ongoing on treatment and 64 (66.7%) were ongoing in the study at the time of 29 May 2020 data cutoff.

NDA: supplemental New Drug Application; U.S., United States.

Figure 8 presents an illustration of the study design, with additional details provided in the subsequent sections.

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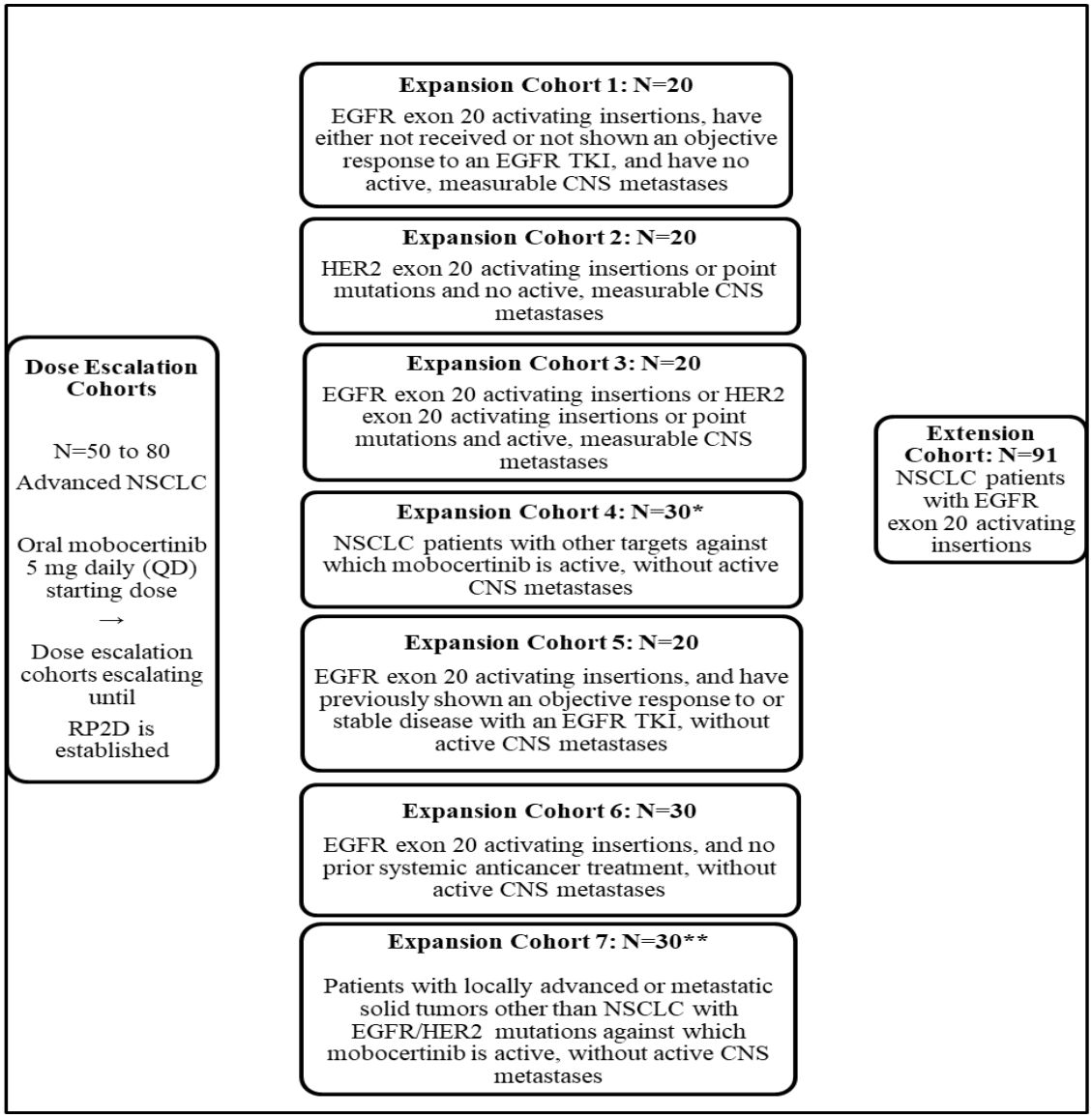
Figure 8: Schematic of Mobocertinib Phase 1/2 Study Design - Dose-Excalation (Part 1), Expansion (Part 2), and Extension (Part 3) Phases



CNS: central nervous system; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor-2; NSCLC: non-small cell lung cancer; RP2D: recommended Phase 2 dose; QD: once daily; TKI: tyrosine kinase inhibitor.

* Cohort 4 was to enroll at least 20 patients with an uncommon activating mutation, either alone or in combination with other *EGFR* mutations except exon 20 insertion mutations.

** Cohort 7 was to enroll at least 20 patients with a *HER2* activating mutation, either alone or in combination with other *EGFR* mutations.

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8.1.1.1.1 Protocol and Protocol Amendments

The original protocol (dated 21 November 2015) was amended 6 times before the data cutoff of 29 May 2020. The study is ongoing.

- Protocol Amendment 1 (Dated 22 March 2017). Amendment 1 included modifications for number of dose levels and patients enrolled in Part 1 of the study to establish the RP2D.
- Protocol Amendment 2 (Dated 02 March 2018). Amendment 2 included updates to the inclusion criterion cutoff for creatinine clearance.
- Protocol Amendment 3 (Dated 03 July 2018). Amendment 3 included 3 additional expansion cohorts, and modifications to the inclusion criteria and sample size for Expansion Cohort 4.
- Protocol Amendment 4 (Dated 11 October 2018). The primary purpose of Amendment 4 was to update the protocol to add Part 3 of the study (a Phase 2 extension cohort).
- Protocol Amendment 5 (Dated 13 August 2019). The primary purpose of amendment 5 was to revise the primary endpoint for Expansion Cohort 6. The primary endpoint for Expansion Cohort 6 was changed from ORR as assessed by the investigator to cORR, per RECIST v1.1, as assessed by the IRC.
- Protocol Amendment 6 (Dated 2 September 2020). The primary purpose of this amendment was to update the per-protocol definition and incorporate changes due to coronavirus disease 2019 (COVID-19).

In addition, Expansion Cohort 3 was closed early because of preliminary results that indicated low efficacy of mobocertinib in this patient population, and Expansion Cohort 7 was closed early because of slow enrollment.

The original protocol, protocol amendments, and the summaries of changes in the protocol amendments are provided in the Study CSR in Module 5.3.5. None of these changes in the amendments affected the endpoints, analyses, or safety evaluations. Changes were routine modifications for study logistics or to ensure that the entry criteria and contraception rules were aligned.

8.1.1.1.2 Statistical Analysis Plan and Amendments

A Statistical Analysis Plan for Study 101 was finalized on 24 Aug 2020. The SAP specified that the primary endpoint was IRC cORR for patients from Parts 1, 2, and 3 treated with 160 mg who a previously received a platinum-based therapy for the NSCLC that harbored exon 20 insertion mutations.

8.1.1.1.3 Interim Analyses

No formal interim analyses or data monitoring were performed for Parts 1 and 2 of the study.

A futility analysis was planned for the primary endpoint for Part 3 when approximately 20 patients had completed their Cycle 4 disease assessment. The study would have been stopped for futility if there was >90% posterior probability that the ORR was less than 25%. The futility

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analysis was conducted on the first 20 patients in the Part 3 full analysis set with a data cutoff of 08 November 2019; the results met the prespecified criteria to continue the study.

8.1.1.1.4 Subject Populations

Pooled Prior Platinum Analysis Set: The Pooled Prior Platinum Analysis Set pooled patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations who had previously been treated with platinum-based chemotherapy (platinum-based chemotherapy is defined as a regimen that consists of a platinum-based chemotherapy agent alone or in combination with other therapies) and who received mobocertinib at the RP2D dose of 160 mg QD from Part 1, Expansion Cohort 1 of Part 2, and Part 3. The Pooled Prior Platinum Analysis Set served as the primary efficacy analysis population.

Full analysis set (for each part of the study): All patients who received at least 1 dose of mobocertinib were included in the full analysis set for each part of the study.

Centrally confirmed analysis set (Part 3): The centrally confirmed analysis set included all patients in Part 3 who have centrally confirmed *EGFR Exon 20* insertion mutations. Sensitivity analyses of efficacy, if estimable, were performed using the centrally confirmed analysis set in Part 3, as well as in the Part 3 expanded analysis set. Additional efficacy analysis, if estimable, were performed in all patients excluding those who had been centrally tested as not having *EGFR Exon 20* insertion mutations in Part 3 and in the Part 3 expanded analysis set.

8.1.1.1.5 Disease Assessment

The study used established RECIST v1.1 criteria for response and progression assessments based on standard imaging (CT or MRI scans) assessed by both the investigator and IRC. The external radiology review committee provided independent verification of radiographic outcomes to confirm the investigator assessments of disease status. Though patients were enrolled based on local laboratory mutation determination, mutation status was centrally confirmed by NGS in the majority of patients.

ORR results were independently confirmed by an IRC, and IRC assessments were not disclosed to investigators. Disease status was assessed every 8-weeks after the initial dose of mobocertinib through Cycle 14 then every 12 weeks thereafter until end of treatment. The frequent and consistent disease status evaluation schedule added to the reliability and accurate timing of confirmed response as well as its durability.

8.1.1.1.6 Primary Efficacy Analyses

Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data, and percentages for categorical data) were used to summarize patient characteristics, treatment administration/compliance, efficacy, safety, and pharmacokinetic parameters. Data was also displayed graphically, where appropriate.

Two-sided exact 95% binomial CIs were computed for all binary efficacy endpoints.

For the primary analysis the best response (CR, PR, SD, or PD) according to RECIST v1.1 was derived for each eligible patient. Patients with no measurable disease at baseline or no adequate postbaseline response assessment were included as nonresponders. cORR was calculated as the proportion of treated patients who were confirmed to have achieved CR or PR after the initiation of study drug. Confirmed responses were those that persist on repeat imaging at least 4 weeks after initial response.

The primary endpoint of cORR, as assessed by the IRC, was tested using exact methods in the full analysis set. Exact 2-sided 95% CIs for the cORR were calculated based on the binomial distribution.

Best percent change in the sum of target lesion diameters was displayed using a “waterfall” plot. Supportive sensitivity analyses were performed for ORR assessed by the IRC in the per-protocol population and using all responses (ie, including unconfirmed responses).

Censoring Rules

The primary endpoint of cORR, as assessed by the IRC. No censoring rules were applied to the analysis of cORR.

PFS and DOR as assessed by the IRC and the investigator were each secondary efficacy endpoints. Censoring rules as per Table 17 were applied to PFS and DOR. These rules are defined consistently with FDA Guidance: “Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics Guidance for Industry” (April 2015).

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Table 17: Schema of Progression and Censoring for Primary Analysis of PFS

Rule	Situation Outcome	Date of progression or	Censoring
1	No baseline disease assessment		Censored, PFS = 1 day
2	No post-baseline disease assessment		Censored, PFS = 1 day
3	No measurable disease at baseline	Date of new lesion(s) or substantial worsening in non-target disease	Progressed
		Date of last adequate progression-free radiographic assessment	Censored
4	Disease progression or death within 126 days of last adequate radiographic assessment	Earliest of date of death or date of disease progression	Progressed
5	Disease progression or death >126 days of last adequate radiographic assessment	Date of last adequate radiographic assessment prior to the 126-day interval	Censored
6	No progression or death	Date of last radiological assessment of measured lesions	Censored
7	New anti-cancer treatment started without documented disease progression and lead to treatment discontinuation	Date of last adequate progression-free radiographic assessment prior to initiation of new anti-cancer treatment	Censored
8	Cancer-related surgery prior to documented disease progression	Date of last adequate progression-free radiographic assessment prior to surgery	Censored
9	Disease progression documented between scheduled visits	Date of progression	Progressed

PFS: progression-free survival.

Censoring in the analysis of DOR was the same as for PFS.

8.1.1.1.7 Sensitivity Analyses of the Primary Endpoint

Not applicable.

8.1.1.1.8 Key Secondary Efficacy Endpoints and Analyses

cORR assessed by the investigator in the full analysis set and the Pooled Prior Platinum Analysis Set were analyzed to assess the robustness of the primary analysis of the primary endpoint.

DCR assessed by the investigator and the IRC in the full analysis set and the Pooled Prior Platinum Analysis Set and the exact 2-sided 95% binomial CIs were calculated.

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For time-to-event efficacy endpoints including PFS, OS, and DOR, survival curves and median values (if estimable), along with their 2-sided 95% CIs were computed using Kaplan-Meier method [47] in the full analysis set and the per-protocol population. The PFS rates, OS rates, and DOR rates and the associated 2-sided 95% CIs were computed using the Kaplan-Meier method. Time to response was summarized only for responders using descriptive statistics.

Exploratory analyses were performed within subgroups defined by age, sex, race, ethnicity, geographic region, smoking status, ECOG performance status, prior immunotherapy, prior EGFR TKI, prior platinum-based chemotherapy, and baseline brain metastasis. In addition to cytotoxic chemotherapy, immunotherapies targeting PD-(L)1 as monotherapies or in combination with platinum-based chemotherapy may be considered available therapy. Exploratory analyses were also performed on a subgroup defined by prior anti-PD (L)1 therapy.

The FDA's Assessment:

The FDA generally agrees with the Applicant's descriptions of the design of Study 101 and the study endpoints. With regards to the secondary endpoints, the FDA does not consider disease control rate (DCR) a clinically meaningful endpoint, and time-to-event efficacy endpoints, including PFS and OS, are uninterpretable in a single-arm study due to a lack of randomized comparator.

8.1.1.2 Supportive RWD from Retrospective Observational Study 5002

The Applicant's Position:

Study 5002 was a retrospective observational study of NSCLC patients with *EGFR Exon 20* insertion mutations to characterize the natural history of disease and describe clinical outcomes in patients with advanced NSCLC harboring *EGFR Exon 20* insertion mutations. This study was a non-interventional retrospective study that did not impose a treatment protocol, any diagnostic/interventional procedure, or a visit schedule.

The major design elements of Study 5002 are summarized in Table 18.

Table 18: Overview of TAK-788-5002

Alternative names for Study	TAK-788-5002
Title	Retrospective Observational Study of Non-Small Cell Lung Cancer (NSCLC) Patients with *EGFR Exon 20* Insertion Mutations: Real World Data Generation of Natural History
NCT	Not applicable
Design and description	A retrospective observational cohort study was conducted in patients with advanced NSCLC with *EGFR Exon 20* insertion mutations to address the objectives of the study. This study used longitudinal data from the Flatiron Health Research Database, a nationwide electronic health record (EHR)-derived de-identified database. The data delivered as part of this study had a cutoff date of 29 Feb 2020 (inclusive). Two study cohorts were identified: TN patients and trial-aligned patients. TN patient

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Table 18: Overview of TAK-788-5002

Alternative names for Study	TAK-788-5002
	cohort consisted of patients who received the first-line therapy in the advanced setting, ie, not undergone any prior treatment for advanced NSCLC. Trial-aligned patient cohort consisted of patients who had been previously treated and whose baseline characteristics were aligned with the key eligibility criteria of the TAK-788 Phase 2 pivotal trial (Study No. AP32788-15-101) Part 3 extension cohort. The index date was defined separately for TN and trial-aligned patients. For TN patients, the index date was defined as the start date of the first-line therapy. For trial-aligned patients, the index date was defined as the start date of the next treatment initiated immediately after a confirmed diagnosis of locally advanced or metastatic NSCLC, documented *EGFR Exon 20* insertion mutations, and ≥1 prior line of therapy in the advanced setting. The baseline period was defined as the 3 months leading up to the index date, which may have encompassed the first confirmed diagnosis of locally advanced or metastatic NSCLC. Patients' baseline characteristics were assessed during this time. The observation period, defined as the duration from index date to the earliest of patient death or end of data availability, was used to assess the various study outcomes of interest.
Primary objective and patient population	The overall objective of this retrospective observational cohort study was to characterize the natural history of disease and describe clinical outcomes in patients with advanced NSCLC harboring epidermal growth factor receptor (EGFR) exon 20 insertion mutations. Primary Objective: To describe the anti-tumor effectiveness of currently used standard of care, based on the following endpoints: All endpoints were assessed separately in each of the 2 patient populations: • TN patients. • Trial-aligned patients. In additional analyses, all endpoints were assessed in the following 2 populations: • Previously treated patients. • Prior platinum trial-aligned patients.
Endpoint	Primary endpoint: • Confirmed rwORR, defined as the proportion of patients on a given treatment that had a partial response (PR) or complete response (CR) assessment determination based on clinical documentation followed by a subsequent assessment of PR, CR or stable disease (SD) during the course of a single line of therapy, among all patients in that cohort. Secondary endpoints: • rwDOR, defined as the time from the date of first CR or PR after treatment initiation to the date of the first noted occurrence of progressive disease (PD) or death; patients were censored at the last known response assessment determination that was CR, PR, or SD during the course of a single line of therapy. rwDOR was estimated among patients with confirmed response. • rwDCR, defined as the proportion of patients who had at least 1 SD, PR, or CR assessment during the course of a single line of therapy, among all patients in that cohort.

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Table 18: Overview of TAK-788-5002

Alternative names for Study	TAK-788-5002
	• OS, defined as the time from the index date to death. Patients for whom a date of death has not been identified, were censored at the date of last confirmed activity (ie, last structured visit date or last abstracted oral end date, whichever occurred last). • rwPFS, defined as the time from the index date to real-world progression or death from any cause; patients were censored at the end of line of therapy or last clinic note date whichever was earlier. • rwTTD, defined as time from treatment initiation to treatment discontinuation for any reason. Treatment discontinuation was defined as the date of the last drug episode during the same treatment line of therapy or death, whichever occurred earlier. Patients were considered to discontinue treatment if they had advanced to a new line of therapy since the last drug episode, had a recorded date of death, or had visit activity more than 120 days after the last drug episode. Patients with no evidence of treatment discontinuation were censored at the end of last drug episode during the same treatment line of therapy. • rwTTNT, defined as time from treatment initiation to death or the day before initiation of the next treatment line, whichever was earlier; patients were censored at the date of the last confirmed activity (ie, last structured visit date or last abstracted oral end date, whichever occurred last).
Sample size	A total of 237 patients with advanced NSCLC harboring exon 20 insertion mutations were collected from the Flatiron database.

NDA: supplemental New Drug Application; U.S., United States.

The FDA's Assessment:

The FDA acknowledges the Applicant's description of Study TAK-788-5002. Due to the limitations of external controls these data are considered supportive and were not independently verified by the FDA.

8.1.2 Study Results

8.1.2.1 Primary Efficacy Analysis from AP32788-15-101 Pooled Prior Platinum Analysis Set

The Applicant's Position:

The efficacy evidence to support this initial NDA uses the Pooled Prior Platinum Analysis Set data cutoff of 01 November 2020 at the request of the Agency.

8.1.2.1.1 Compliance with Good Clinical Practices

Study 101 was performed in accordance with Good Clinical Practice.

The investigator was instructed not to deviate from the protocol except where necessary to eliminate an immediate hazard to study subjects. The site documented all protocol deviations in

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the subject's source documents. The Applicant assessed any protocol deviation; if it was likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it was reported to regulatory authorities as a serious breach of Good Clinical Practice and the protocol.

8.1.2.1.2 Financial Disclosure

All investigators were assessed for equity interest, significant payments, proprietary interest, and other compensation. Of the 622 clinical investigators involved in Study 101, financial disclosure forms were obtained for 621 (99.8%) investigators. There is 1 sub-investigators (0.2%) who did not have a financial disclosure form available. Takeda acted with due diligence to obtain financial disclosure information for this sub-investigators. The site informed Takeda that the sub-investigator is no longer at the site and that a financial disclosure form was not completed.

Overall 607 (97.6%) investigators who provided financial disclosure forms do not have any disclosable financial information, and 1 (0.2%) investigators did not have a financial disclosure form available. Of the 622 investigators, 14 (2.3%) have disclosable financial information and Form FDA 3455 has been submitted for each of them. Among the 14 investigators, 6 of them provided financial disclosure forms and confirmed their financial interests exceeding $25,000. There are 8 investigators whose collected financial disclosure forms disclose no financial interested, however based on a verification of Takeda internal financial records and direct payments these investigators had disclosable financial interests or arrangements exceeding $25,000. Takeda has been acting with due diligence to obtain updated financial disclosure information for these investigators. Takeda has appropriate measures in place to minimize potential bias of clinical study results.

8.1.2.1.3 Patient Disposition

A total of 114 patients from Study 101 were included in the Pooled Prior Platinum Analysis Set as of 01 November 2020. Patients in the Pooled Prior Platinum Analysis Set were administered the recommended dose of 160 mg QD (Part 1 [n = 6]; Expansion Cohort 1 of Part 2 [n = 22]; and Part 3 [n = 86]).

8.1.2.1.4 Protocol Violations/Deviations

In Part 1 and 2 at time of the 29 May 2020 data cutoff, a total of 51 patients (24.4%) experienced at least 1 significant protocol deviation. The most frequently occurring significant protocol deviations were related to concomitant medications (9.1%) No significant adverse events were reported associate with the prohibited medications.

In Part 3 at time of the 29 May 2020 data cutoff, a total of 32 patients (33.3%) experienced at least 1 significant protocol deviation. Significant protocol deviations are summarized in

Table 19.

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Table 19: Significant Protocol Deviations - Extension Cohort (Part 3, Full Analysis Set; Data Cutoff 29 May 2020)

	Number of Patients (%)
	Mobocertinib 160 mg QD (Part 3) (N = 96)
Patients with at least 1 significant protocol deviation [a]	32 (33.3)
Entry criteria	5 (5.2)
Concomitant medication	14 (14.6)
Procedure not performed per-protocol	9 (9.4)
Study medication	3 (3.1)
Withdrawal criteria	0
Other	6 (6.3)

Source: Study 101 Table 15.1.4.b Data cutoff: 29 May 2020.

[a] Patients with 1 or more significant protocol deviations within a category are counted only once in that category.

None of these deviations were considered to have an impact on the efficacy or safety conclusions of the study.

8.1.2.1.5 Treatment Compliance, Concomitant Medications, and Rescue

Mobocertinib was self-administered, and patients were provided a diary card or equivalent where the date of study drug administration was recorded. Overall treatment compliance was assessed as a reflection of exposure to study drug (Section 8.2.2.1).

In the Pooled Prior Platinum Analysis Set, the median dose intensity was 156.65 mg/day, with a relative dose intensity of 51.2% to 100.0% at the May 2020 data cutoff. Overall compliance rates were over 80% across all instruments with the majority of cycles reaching compliance rates >90%.

8.1.2.1.6 Efficacy Results

In view of the median time on study for the Pooled Prior Platinum Analysis Set at the 29 May 2020 data cutoff (8.76 months), and considering the time to response, the primary endpoint of cORR is mature. The cORR in the Pooled Prior Platinum Analysis Set was 26.3% by IRC assessment (Table 20), which demonstrates that mobocertinib is highly active in patients with NSCLC with *EGFR Exon 20* insertion mutations who were previously treated with platinum-based chemotherapy.

To further characterize the clinical benefit of mobocertinib in the Pooled Prior Platinum Analysis Set, efficacy was evaluated from a later data cutoff of 01 November 2020, which forms the primary basis to support the initial registration of mobocertinib.

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At the November 1, 2020 data cutoff, all patients from the 29 May 2020 data cutoff had the opportunity to be followed for an additional 6 months. At the data cutoff of 01 November 2020, 100% and 93.8% of responders, as assessed by investigator and IRC, respectively, had at least 6 months of follow-up after onset of response. Results from this data cutoff, together with the results from the 29 May 2020 data cutoff, are summarized in Table 20 with results of the prior Anti-PD-(L)1 subgroups in Table 21 (IRC assessment) and Table 22 (investigator assessment).

Efficacy results from the Pooled Prior Platinum Analysis Set continued to demonstrate a clinically meaningful treatment effect, as evident by the consistent response rate and more mature and longer observed DOR, compared with the results of the May 2020 data cutoff. With a median follow-up time of 14.16 months at the November 2020 data cutoff, the cORR by IRC assessment was 28.1%, while the cORR was 26.3% at the May 2020 data cutoff. The improvement of IRC-assessed cORR was due to 2 additional responders from the Part 3 cohort who were confirmed by the IRC after the 29 May 2020 data cutoff. The investigator-assessed cORR from the November 2020 data cutoff was the same as that at the May 2020 data cutoff (35.1%). Of note, 1 confirmed PR by investigator assessment deepened to a confirmed CR after the 29 May 2020 data cutoff.

Patients continued to show durable response at the 01 November 2020 data cutoff, with a median DOR of 17.48 months by IRC with Kaplan-Meier methods (Table 20 and Figure 9). DCR and PFS results continued to demonstrate noteworthy control of disease (78.1% and 7.29 months by IRC assessment, respectively). At the time of the data cutoff, 40.4% of patients had died. The median OS was 23.95 months (Table 20 and Figure 10).

A consistent treatment effect was observed in patients with or without prior PD-(L)1 treatment (cORR of 25.0% vs 30.3% by IRC, respectively, and patients with response lasting ≥6 months are 60.0% vs 58.3% by descriptive statistics, respectively) (Table 21). Results in the other subgroups were consistent with the results at the 29 May 2020 data cutoff.

The results by investigator assessment were supportive and similar to the May 2020 data cutoff.

With the additional 6 months of follow-up mobocertinib continues to provide clinically meaningful efficacy while still maintaining a consistent safety profile and offering convenience for patients.

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Table 20: Summary of Efficacy Endpoint Results From the November 2020 and May 2020 Data Cutoffs (Pooled Prior Platinum Analysis Set)

	01 November 2020 (N = 114)		29 May 2020 (N = 114)	
	IRC	Investigator	IRC	Investigator
cORR, n (%) [95% CIs] [a]	32 (28.1) [a] [20.06, 37.26]	40 (35.1) [26.38, 44.59]	30 (26.3) [18.51, 35.39]	40 (35.1) [26.38, 44.59]
Complete response, n(%)	0	1 (<1)	0	0
Partial response, n (%)	32 (28.1) [a]	39 (34.2)	30 (26.3)	40 (35.1)
Confirmed DCR, n (%) [95% CIs] [b]	89 (78.1) [69.35, 85.28]	89 (78.1) [69.35, 85.28]	89 (78.1) [69.35, 85.28]	89 (78.1) [69.35, 85.28]
Duration of confirmed response (KM estimate), median (months) [95% CIs] [c]	17.48 [7.39, 20.30]	11.17 [5.55, NE]	17.48 [8.31, NE]	13.90 [5.55, NE]
KM estimates for duration of confirmed response, (95% CI)				
6 months	71.92 (51.55, 84.88)	66.41 (49.22, 78.95)	78.03 (57.27, 89.54)	65.76 (46.47, 79.52)
12 months	57.71 (35.52, 74.68)	49.68 (31.23, 65.66)	56.89 (26.26, 78.83)	59.79 (38.75, 75.65)
Descriptive duration of confirmed response [d]				
≥6 months, n (%)	19 (59.4)	25 (62.5)	10 (33.3)	13 (32.5)
≥12 months, n (%)	6 (18.8)	8 (20.0)	4 (13.3)	6 (15.0)
PFS, median (months) [95% CIs]	7.29 [5.52, 9.23]	7.33 [5.55, 8.84]	7.29 [5.52, 10.15]	7.29 [5.55, 8.11]
OS, median (months) [95% CIs]	23.95 [14.55, 28.81]		-	

Table 20: Summary of Efficacy Endpoint Results From the November 2020 and May 2020 Data Cutoffs (Pooled Prior Platinum Analysis Set)

	01 November 2020 (N = 114)		29 May 2020 (N = 114)	
	IRC	Investigator	IRC	Investigator
Median follow-up time (months) [95% CIs]	14.16 [13.17, 14.62]		-	
Time on study, median (months) [min, max]	13.01 [1.2, 36.1]		8.76 [1.2, 31.2]	

Source: Study 101 Table 15.1.3D, 15.2.1D, 15.2.2D, 15.2.10D, 15.2.11D, 15.2.11.8D, 15.2.11.9D, 15.2.12D, and 15.2.13D. Data cutoff: 29 May 2020.

Study 101 November 2020 Table 15.1.3D, 15.2.1D, 15.2.2D, 15.2.10D, 15.2.11D, 15.2.11.8D, 15.2.11.9D, 15.2.12D, 15.2.13D, and 15.2.14D. Data cutoff: 01 November 2020.

cORR: confirmed objective response rate; DCR: disease control rate; EGFR: epidermal growth factor receptor; IRC: independent review committee; KM: Kaplan-Meier; max: maximum; min: minimum; NE: not estimable; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival.

Dashes (-) indicate that the analysis was not conducted.

Pooled Prior Platinum Analysis Set: patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations who had previously been treated with platinum-based chemotherapy from Part 1 (treated at the recommended dose), Expansion Cohort 1 of Part 2, and Part 3.

All investigator-assessed confirmed responders had a minimum of 6 months response follow-up at the November 2020 data cutoff, and 30 of the 32 IRC-assessed confirmed responders (93.8%) had a minimum of 6 months response follow-up at the November 2020 data cutoff (Study 101 November 2020 Table 15.2.11.10D).

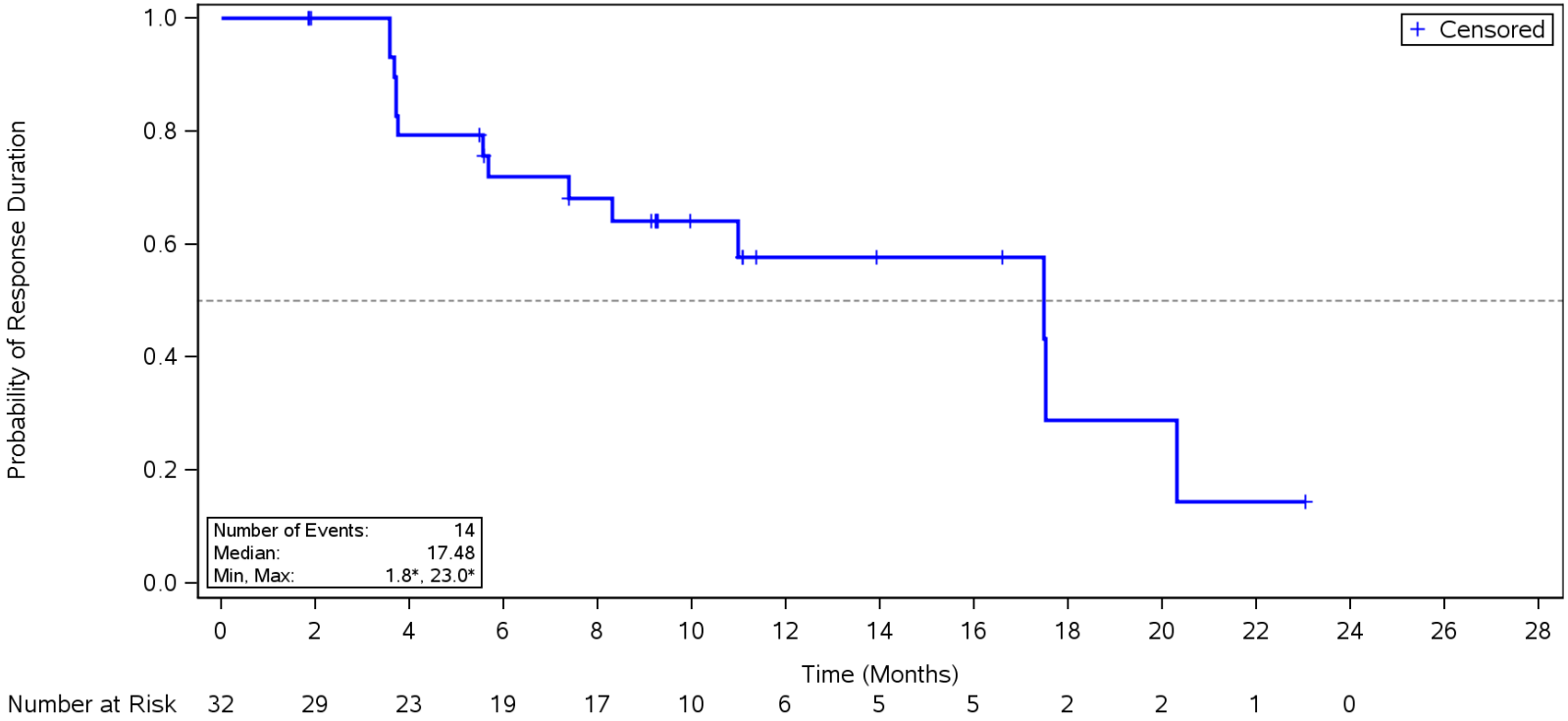
[a] The improvement of IRC-assessed cORR was due to 2 additional responders from the Part 3 cohort who were confirmed by the IRC after the May 2020 data cutoff.

[b] Exact Clopper-Pearson CIs of the percentage.

[c] Estimated using KM analyses in confirmed responders only.

[d] Descriptive statistics in confirmed responders only.

Figure 9: Kaplan-Meier Plot of IRC-Assessed DOR (Pooled Prior Platinum Analysis Set) - 01 November 2020 Data Cutoff



Source: Study 101 November 2020 Figure 15.2.5.1D. Data cutoff: 01 November 2020.
DOR: duration of response; IRC: independent review committee; Max: maximum; Min: minimum.

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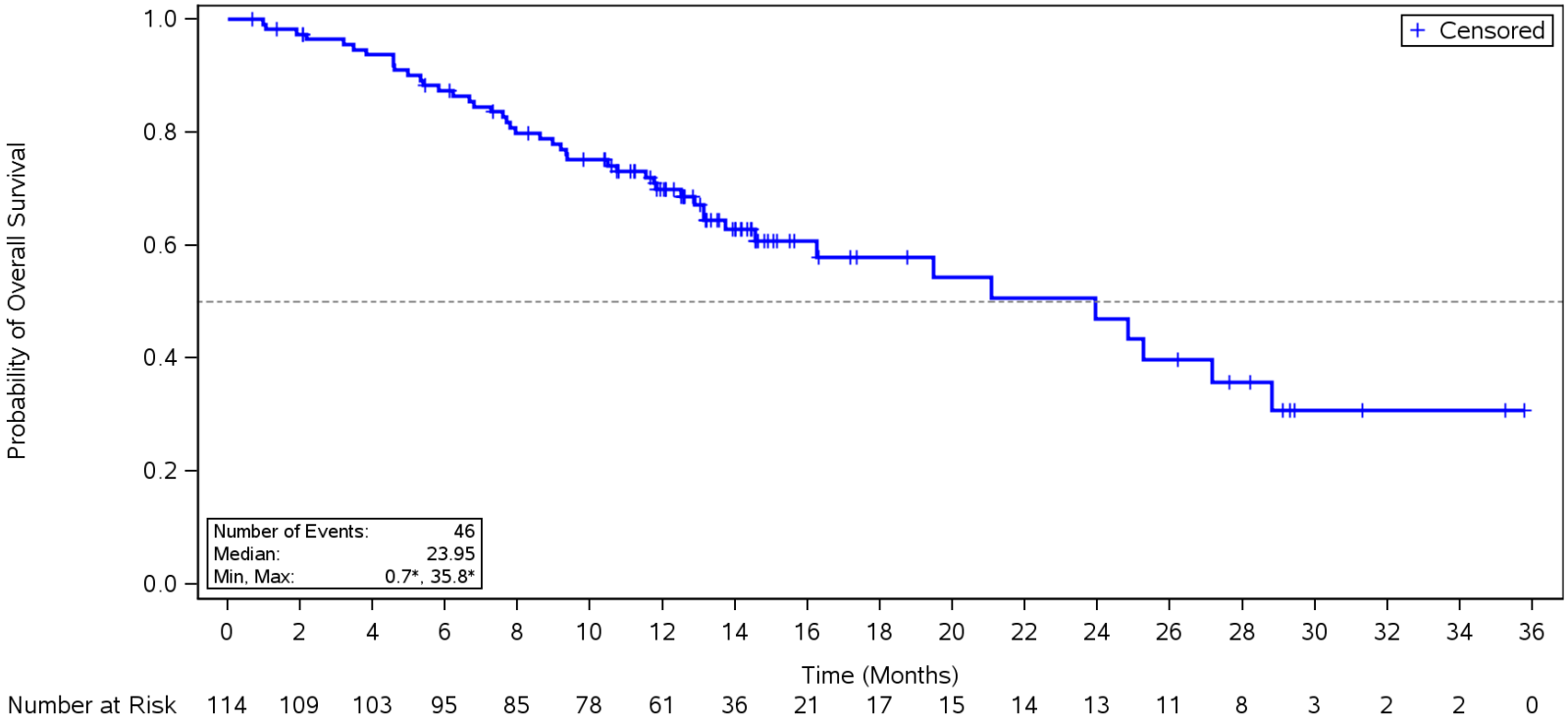
Figure 10: Kaplan-Meier Plot of Overall Survival (Pooled Prior Platinum Analysis Set) - 01 November 2020 Data Cutoff



Source: Study 101 November 2020 Figure 15.2.6D. Data cutoff: 01 November 2020.
Max: maximum; Min: minimum.

Table 21: IRC-Assessed cORR and DOR for Pooled Prior Platinum Analysis Set and Subgroups With or Without Prior Anti PD-(L)1 Antibody

	01 November 2020			29 May 2020		
	Patients Without Prior Anti-PD-(L)1 Antibody (N = 66)	**Patients With Prior Anti-PD-(L)1 Antibody (N = 48)**	**Overall (N = 114)**	**Patients without Prior Anti-PD-(L)1 Antibody (N = 66)**	**Patients with Prior Anti-PD-(L)1 Antibody (N = 48)**	**Overall (N = 114)**
cORR, n (%)	**20 (30.3)**	**12 (25.0)**	**32 (28.1)**	**18 (27.3)**	**12 (25.0)**	**30 (26.3)**
(95% CI)	(19.59, 42.85)	(13.64, 39.60)	(20.06, 37.26)	(17.03, 39.64)	(13.64, 39.60)	(18.51, 35.39)
Confirmed DCR, n (%)	**52 (78.8)**	**37 (77.1)**	**89 (78.1)**	**52 (78.8)**	**37 (77.1)**	**89 (78.1)**
(95% CI)	(66.98, 87.89)	(62.69, 87.97)	(69.35, 85.28)	(66.98, 87.89)	(62.69, 87.97)	(69.35, 85.28)
Descriptive DOR (months)						
Median (95% CI)	7.85 (3.71, 9.95)	9.23 (5.49, 17.51)	8.72 (5.55, 10.97)	4.65 (3.71, 6.01)	5.57 (3.71, 17.51)	5.55 (3.71, 6.01)
Min, max	1.8, 17.5	3.6, 23.0	1.8, 23.0	1.8, 17.5	3.6, 20.3	1.8, 20.3
≥3 months, n (%)	17 (85.0)	12 (100.0)	29 (90.6)	17 (94.4)	12 (100.0)	29 (96.7)
≥4 months, n (%)	13 (65.0)	10 (83.3)	23 (71.9)	9 (50.0)	8 (66.7)	17 (56.7)
≥5 months, n (%)	13 (65.0)	10 (83.3)	23 (71.9)	9 (50.0)	8 (66.7)	17 (56.7)
≥6 months, n (%)	12 (60.0)	7 (58.3)	19 (59.4)	5 (27.8)	5 (41.7)	10 (33.3)
≥12 months, n (%)	2 (10.0)	4 (33.3)	6 (18.8)	1 (5.6)	3 (25.0)	4 (13.3)

Source: Study 101 Table 15.2.2D, 15.2.2.7D, and 15.2.11.9D. Data cutoff: 29 May 2020.

Study 101 November 2020 Table 15.2.2D, 15.2.2.7D, and 15.2.11.9D. Data cutoff: 01 November 2020.

cORR: confirmed objective response rate; DCR: disease control rate; DOR: duration of response; IRC: independent review committee; PD-(L)1: programmed cell death protein 1 or programmed death-ligand 1.

Prior treatment with Anti-PD-(L)1 antibody can be either concurrent or sequential with prior treatment of platinum-based chemotherapy.

Table 22: Investigator-Assessed cORR and DOR for Pooled Prior Platinum Analysis Set and Subgroups With or Without Prior Anti PD-(L)1 Antibody

	01 November 2020 (N = 114)			29 May 2020 (N = 114)		
	Patients Without Prior Anti-PD-(L)1 Antibody (N = 66)	**Patients With Prior Anti-PD-(L)1 Antibody (N = 48)**	**Overall (N = 114)**	**Patients Without Prior Anti-PD-(L)1 Antibody (N = 66)**	**Patients With Prior Anti-PD-(L)1 Antibody (N = 48)**	**Overall (N = 114)**
cORR, n (%)	**22 (33.3)**	**18 (37.5)**	**40 (35.1)**	**22 (33.3)**	**18 (37.5)**	**40 (35.1)**
(95% CI)	(22.20, 46.01)	(23.95, 52.65)	(26.38, 44.59)	(22.20, 46.01)	(23.95, 52.65)	(26.38, 44.59)
Confirmed DCR, n (%)	**52 (78.8)**	**37 (77.1)**	**89 (78.1)**	**52 (78.8)**	**37 (77.1)**	**89 (78.1)**
(95% CI)	(66.98, 87.89)	(62.69, 87.97)	(69.35, 85.28)	(66.98, 87.89)	(62.69, 87.97)	(69.35, 85.28)
Descriptive DOR (months)						
Median (95% CI)	9.23 (7.00, 11.07)	6.54 (5.39, 13.93)	9.22 (5.55, 11.07)	5.55 (3.75, 6.01)	5.44 (3.84, 13.90)	5.52 (4.96, 5.59)
Min, max	3.2, 19.3	3.7, 24.9	3.2, 24.9	3.2, 19.3	3.7, 22.1	3.2, 22.1
≥3 months, n (%)	22 (100.0)	18 (100.0)	40 (100.0)	22 (100.0)	18 (100.0)	40 (100.0)
≥4 months, n (%)	19 (86.4)	15 (83.3)	34 (85.0)	15 (68.2)	12 (66.7)	27 (67.5)
≥5 months, n (%)	19 (86.4)	14 (77.8)	33 (82.5)	15 (68.2)	11 (61.1)	26 (65.0)
≥6 months, n (%)	16 (72.7)	9 (50.0)	25 (62.5)	6 (27.3)	7 (38.9)	13 (32.5)
≥12 months, n (%)	2 (9.1)	6 (33.3)	8 (20.0)	1 (4.5)	5 (27.8)	6 (15.0)

Source: Study 101 Table 15.2.1D, 15.2.2.6D, and 15.2.11.8D. Data cutoff: 29 May 2020.
Study 101 November 2020 Table 15.2.1D, 15.2.2.6D, and 15.2.11.8D. Data cutoff: 01 November 2020.
cORR: confirmed objective response rate; DCR: disease control rate; DOR: duration of response; PD-(L)1: programmed cell death protein 1 or programmed death-ligand 1.
Prior treatment with Anti-PD-(L)1 antibody can be either concurrent or sequential with prior treatment of platinum-based chemotherapy.

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The FDA's Assessment:

FDA agrees with the Applicant's description of the results of the primary and key secondary analyses of Study 101 based on a data cutoff date of November 1, 2020. FDA considers the analyses related to DCR to be exploratory and did not verify the DCR results. FDA considers time-to-event endpoints to be uninterpretable in a single arm study; therefore, statistical analyses of PFS and OS were considered descriptive and were not verified.

The primary efficacy population in Study 101 is generally representative of the intended patient population, e.g., patients with locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy; see Section 13.0 Postmarketing Requirements and Commitment. The 114 patients in the primary efficacy population had a median age of 60 years (range: 27 to 84). A total of 7% were ≥ 75 years of age, 66% were female, 60% were Asian, and 37% were White. Patients had an ECOG status of 0 (25%) or 1 (75%).

Patients included in the primary efficacy population predominantly had Stage IV disease (99%) at initial diagnosis, with 35% having a history of prior brain metastases. In addition to prior platinum-based chemotherapy, 43% of patients in this population received prior immunotherapy and 25% received prior TKI therapy.

All patients who achieved an IRC-assessed objective response had partial responses. As of the November 1, 2020 data cutoff date, 59% of the responders had a duration of response of ≥ 6 months, 19% had a duration of response for ≥ 12 months, and 16 patients (14%) had ongoing responses. The median duration of response as assessed by IRC based on Kaplan Meier estimates, was 17.5 months (95% CI: 7.4, 20.3).

EGFR exon 20 insertion mutation status was determined based on local testing. Of the 114 patients in the primary efficacy population, central confirmation of EGFR exon 20 insertion mutations (by ODxT) was available for 60 patients (53%). The confirmed ORR in these patients was 27% (95% CI 16, 40) and the median DOR was 17.5 months (95% CI: 3.7, not reached). The remaining 54 patients either had negative test results or were unable to have ODxT test performed.

Given that the primary efficacy analysis data cutoff date was November 1, 2020, the FDA did not independently verify data from May 2020.

Protocol Deviations

According to the Applicant, 38 patients (33%) from the primary efficacy population had at least one significant protocol violation (Table 23). The majority of the significant protocol violations were for use of prohibited concomitant medications (n=27, 24%) or procedures not performed per protocol (n=10, 9%). Of the patients with violations for procedures not performed per protocol, only one was imaging related and involved a missed MRI of the lower extremity. Most

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of the remaining violations of procedures not performed per protocol were related to continuing therapy despite toxicities, due to patient decision, investigator decision, or errors in assigning grades to lab values. FDA agrees with the Applicant that the reported protocol deviations are not expected to pact the interpretability of the study results.

There were three significant protocol violations related to SARS-coronavirus-2 (COVID-19). Two were from a single patient with COVID-19 who took Plaquenil and azithromycin, both of which were prohibited medications. The third was the missed MRI of the lower extremity, as described above.

Table 23: Significant protocol deviations, primary efficacy population (FDA table)

	Number of patients (%) Primary efficacy population (n=114)
Patients with at least 1 significant protocol deviation[a]	38 (33)
Entry criteria	3 (2.6)
Concomitant medication	27 (24)
Procedure not performed per protocol	10 (9)
Study medication	3 (2.6)
Withdrawal criteria	0
Other	1 (0.9)

Source: Table 15.1.4D; 01 November 2020 data cutoff

[a]Patients with one or more significant protocol deviations within a category are counted only once in that category

In addition, Protocol Amendment 6 (September 2, 2020) incorporated changes due to the COVID-19 public health emergency including direct-to-patient (DTP) dispensing as an alternative method of dispensing self-administered study drug, alternative methods for conducting patient visits, electronic informed consent language, and accommodations to allow local disease assessments.

8.1.2.1.7 Patient-Reported Outcomes (PRO)

Patient-reported outcomes (PRO) were recorded only in patients enrolled to Part 3 of Study 101.The core symptoms of lung cancer, including dyspnoea, cough, and chest pain, as measured by the EORTC QLQ-LC13 linear mixed model, improved from baseline. As shown in Figure 11, improvements in each of the dyspnoea, cough, and chest pain domains were seen as early as Cycle 2 and maintained during treatment. Notably, improvements from baseline in most of the time cycles were significant ($p<0.001$) through Cycle 10 (Figure 11).

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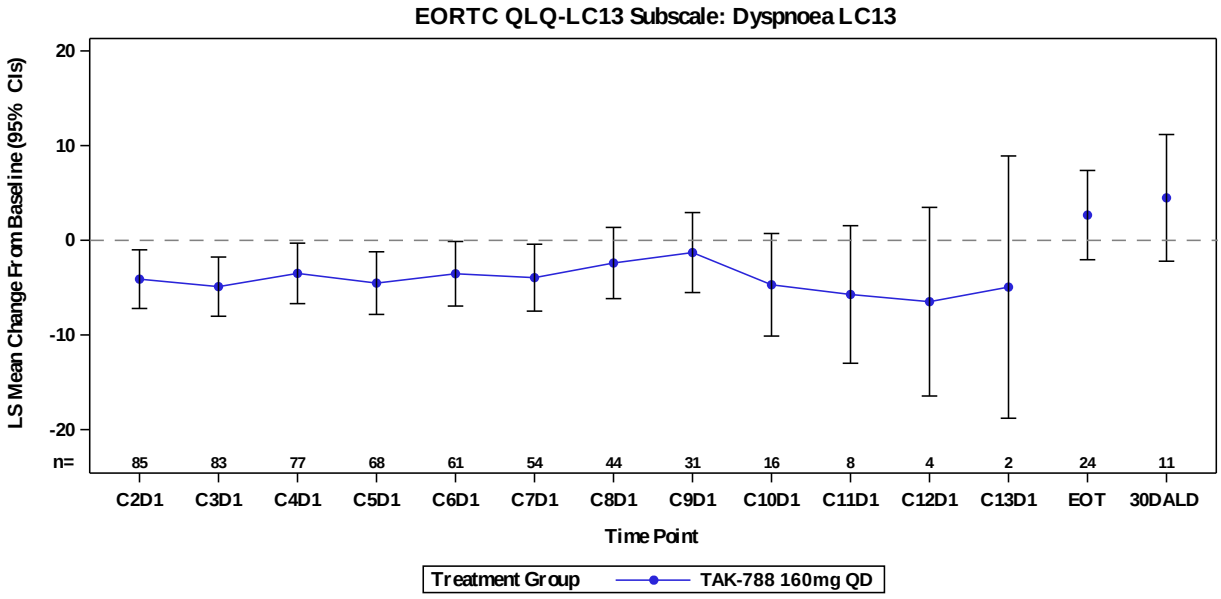
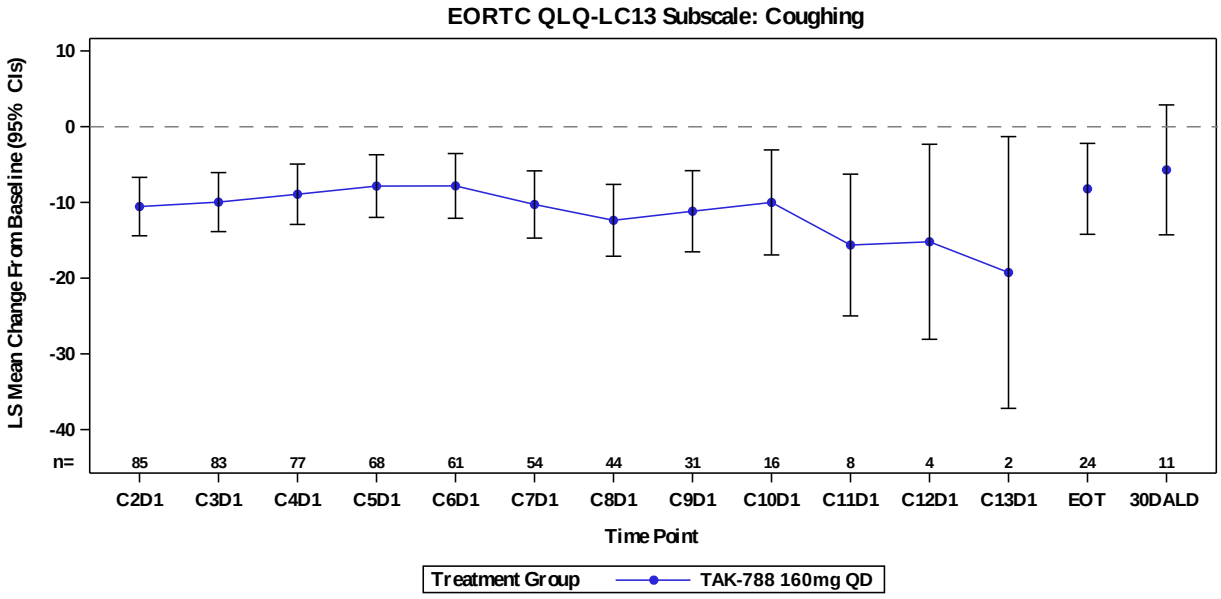
Figure 11: Plot of EORTC QLQ-LC13 Scores Change from Baseline using Linear Mixed Models (Part 3, PRO Full Analysis Set; Data Cutoff 29 May 2020)





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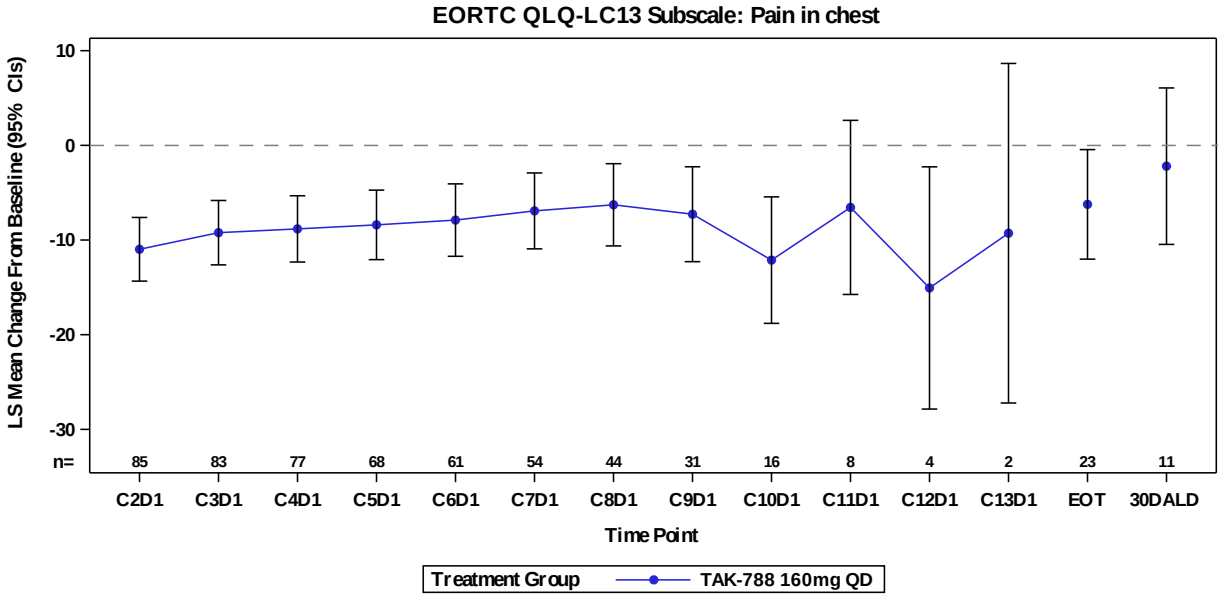

Source: Study 101 Figure 15.3.13.b. Data cutoff: 29 May 2020.

30DALD: 30 Days After Last Dose; C: Cycle; D: day; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, lung cancer module; EOT: End-of-Treatment; LS: least-squares; PRO: patient-reported outcome; QD: once daily; TAK-788: mobocertinib.

PRO-CTCAE frequency, severity, and interference were assessed for worst reported in the first 24 weeks. Similar to the physician-reported AEs, frequent diarrhoea was experienced in a majority (54.54%) of patient-reported CTCAEs. Additionally when asked the worst severity of adverse effects during the first 24 weeks of treatment, more than one-third of patients reported dry skin (38.63%) to be “severe” or “very severe.” The majority of patients did not report other adverse effects as “frequent,” “severe,” or interfering “quite a bit” with usual or daily activities or worse.

A summary of EQ-5D-5L scores demonstrated that patient-reported health status was maintained (Figure 12).

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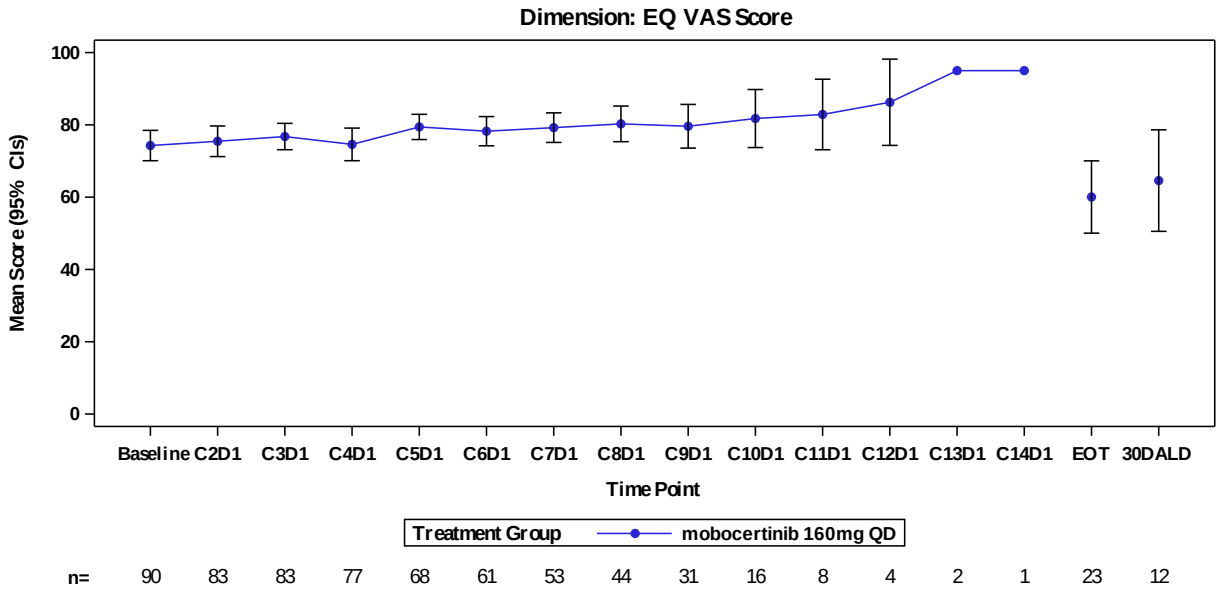
Figure 12: Plot of EQ-5D-5L VAS Mean Scores (Part 3, PRO Full Analysis Set; Data Cutoff 29 May 2020)



Source: Study 101 Figure 15.3.17.b. Data cutoff: 29 May 2020.
30DALD: 30 Days After Last Dose; C: Cycle; D: day; EQ-5D-5L: EuroQol 5-Dimensions 5-Levels questionnaire; EOT: End-of-Treatment; PRO: patient-reported outcome; VAS: Visual Analogue Scale.

Global health status/quality of life, physical functioning, emotional functioning, role functioning, cognitive functioning, and fatigue were maintained throughout therapy.

The FDA's Assessment

FDA considers the analyses of patient-reported outcome (PRO) endpoints to be exploratory. No claims can be made based on these analyses, which are based on a subset of the primary efficacy population. There was no prior agreement between the Applicant and the FDA on the analysis plan for these endpoints or on the establishment of a threshold for improvement from baseline that would be considered clinically meaningful, and the non-randomized open-label nature of the study limits the interpretation of the observed results.

8.1.2.1.8 Dose/Dose Response

PK data collected in Parts 1, 2, and 3 of Study 101 contributed to population PK and exposure-response (safety and efficacy) analyses. The results of these analyses are summarized in Section 6.2.2.

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8.1.2.1.9 Persistence of Effect

In all parts of Study 101, mobocertinib was dosed until PD that required an alternate therapy, intolerable toxicity, or another discontinuation criteria was met. Study drug was usually discontinued once the patient had disease progression; approximately 65% of patients discontinued due to PD according to RECIST v1.1 or clinical progression in Part 3 and in the Pooled Prior Platinum Analysis Set.

8.1.2.1.10 Integrated Review of Effectiveness

The pivotal efficacy results from the Pooled Prior Platinum Analysis Set are based on a data cutoff of 01 November 2020 to add to the characterization of the clinical benefit of mobocertinib in NSCLC patients with EGFR exon20 insertion mutations who have been previously treated with platinum-based chemotherapy. The pooled efficacy results, as presented in Section 8.1.2.1.6, forms the primary basis to support the integrated review of effectiveness.

<u>The FDA's Assessment:</u>

The efficacy evaluation for this submission is primarily based on the analysis of the 114 patients enrolled across Study 101 who received prior platinum-based chemotherapy. This population was selected as the primary efficacy population as standard first-line therapy for patients with NSCLC with EGFR exon 20 insertion mutations is platinum-based chemotherapy with or without an anti-PD-(L)1 agent. Given that the first patient provided informed consent to participate in Study 101 on June 8, 2016, prior to the approvals of anti-PD-(L)1 agents for the first line treatment of patients with metastatic NSCLC, and therefore before the widespread adoption of anti-PD-(L)1 agents as part of the standard of care, choosing a population of patients who had received prior platinum-based chemotherapy was most reflective of the intended NSCLC population with EGFR exon 20 insertion mutations at the time of study conduct. Additionally, the subgroup analyses of ORR in the populations of patients in the primary efficacy population who received a prior anti-PD-(L)1 agent (n=48) and those who did not receive a prior anti-PD-(L)1 agent (n=66) were similar, with ORRs of 25% (95% CI 14, 40) and 30% (95% CI 20, 43), respectively with a consistent treatment effect observed in durability. This suggests that the efficacy of mobocertinib in patients with NSCLC with EGFR exon 20-mutations is consistent irrespective of receipt of prior immunotherapy.

The primary evidence of effectiveness of mobocertinib was established by the demonstration of a clinically meaningful durable ORR in the primary analysis population comprising 114 patients with EGFR exon 20 insertion mutation-positive NSCLC whose disease had progressed on or after platinum-based chemotherapy in Study 101. The ORR per IRC assessment was 28% (95% CI: 20, 37); as of the November 1, 2020 data cut-off date, the median DOR was 17.5 months (range: 7.4, 20.3). Additionally, 59% of responders had a response that lasted six months or longer and 19% of responders had a response that lasted 12 months or longer. At the data-cutoff, the response was ongoing for 16 responders. Subgroup analyses (ORR by race, age, gender, ECOG status, and prior anti-PD (L)1 treatment status) were consistent with the primary efficacy results and are provided in Table 24. Although there were numeric differences in the ORRs

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observed between patients <65 years vs. ≥ 65 years (32% vs. 21%) and Asian patients vs. White patients (31% vs. 21%), the subgroups are small and the 95% confidence intervals around the point estimates of the ORRs are widely overlapping, so it is not possible to draw conclusions about differences in the efficacy of mobocertinib across subgroups.

Table 24: Objective response rates by subgroup (FDA table)

Subgroup	**N**	**ORR % (95% CI)**
Age		
<65 years	72	31.9 (21.4, 44.0)
≥ 65 years	42	21.4 (10.3, 36.8)
Sex		
Female	75	29.3 (19.4, 41.0)
Male	39	25.6 (13.0, 42.1)
Race		
Asian	68	30.9 (20.2, 43.3)
White	42	21.4 (10.3, 36.8)
Black	3	33.3 (0.8, 90.6)
Region		
Asia Pacific	55	29.1 (17.6, 42.9)
Europe	6	33.3 (4.3, 77.7)
North America	53	26.4 (15.3, 40.3)
Overall	114	28.1 (20.1, 37.3)

The FDA agrees with the Applicant that the results from the primary efficacy population from Study 101 provide substantial evidence of effectiveness and support accelerated approval of

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mobocertinib for patients with advanced NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

Progression-free survival results are difficult to interpret in a non-randomized, open label study without a control, and therefore are considered exploratory in Study 101.

8.1.2.2 Analysis of RWD for Previously Treated NSCLC Patients with EGFR Exon 20 Insertion Mutations

The Applicant's Position:

The analysis of RWD for previously treated NSCLC patients with *EGFR Exon 20* insertion mutations are supportive efficacy analyses to the primary efficacy analysis from the Pooled Prior Platinum Analysis Set, which are summarized in Section 8.1.2.1.

Study 5002

Because of the rarity of *EGFR Exon 20* insertion mutations and the fact that there is no approved targeted therapy in this rare population, there is no current standard of care for these patients and thus the treatment outcomes are not well established. Evidence about the efficacy of other agents in this patient population is scarce. To address these challenges and support single-arm clinical study data, the Applicant collected and conducted analysis of RWD on patients with NSCLC and *EGFR Exon 20* insertion mutations as a historical benchmark (Study TAK-788-5002). This analysis included 2 cohorts of relevance to the efficacy results in Study 101:

- A cohort of study-aligned patients, defined as patients whose baseline characteristics were aligned with the key eligibility criteria of Part 3 of Study 101, who initiated the next treatment after a confirmed diagnosis of advanced NSCLC, had documented *EGFR Exon 20* insertion mutations, and had ≥1 prior line of therapy in the advanced setting (n = 63).
- A cohort of study-aligned patients (as defined above) who had previously received platinum-based chemotherapy (n = 50).

For study-aligned patients (n = 63) and prior platinum study-aligned patients (n = 50) who received any treatment type in the second-line or greater setting in Study TAK-788-5002, real-world cORR (11.1% and 14.0%, respectively), real-world DCR (47.6% and 44.0%, respectively), and real-world PFS (median 3.4 and 3.3 months, respectively) were consistently poor (Table 2.a). The median OS was 13.6 and 11.5 months, respectively. Of note, the cORRs for immuno-oncology monotherapy were 4.8% and 5.0% in study-aligned patients (N = 21) and prior-platinum study-aligned patients (N = 20), respectively. Considering real-world evidence, there was a clear unmet medical need for improved therapeutic options for these patients.

Literature Review of RWD

RWD from China in the literature were also reviewed for patients whose tumors harbor *EGFR Exon 20* insertion mutations. The historical benchmark was similar to that of the historical

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benchmark from the Flatiron Health EMR database in Study TAK-788-5002. In China, the ORR from RWD was 17.1% for second-line chemotherapy and 5.9% for second-line EGFR TKIs [48].

Another study in the literature presented clinical outcomes for PFS and OS for patients with NSCLC harboring *EGFR Exon 20* insertion mutations from the U.S. Flatiron Health database. The results were consistent with TAK-788-5002. The median PFS in the second-line setting was 3.2 months, and the median OS was 13.3 months [34].

German Chart Review from Study 5008

The Applicant collaborated with academic investigators to conduct a retrospective chart review in Germany. Longitudinal data were collected and analyzed from patients with NSCLC with *EGFR* and *HER2* exon 20 insertion mutations from 12 academic thoracic oncology centers across Germany. The cORR was 5% (N = 57) for patients with *EGFR Exon 20* insertion mutation-positive NSCLC who received any therapy type in the second-line setting.

Review of Second-line or Greater Immunotherapy

The Applicant also collected and analyzed literature, health system clinical data, and prior therapy data from Study 101 on patients with NSCLC and *EGFR Exon 20* insertion mutations who were treated with immuno-oncology monotherapy in the second-line or greater setting (second-line immunotherapy white paper in Module 5 of the NDA). On the basis of the results of the meta-analysis, immuno-oncology monotherapy is not an appropriate standard of care therapy for the treatment of these patients. The ORR was 3.5% based on the meta-analysis. (Table 1).

Docetaxel is Standard of Care

Docetaxel monotherapy or in combination with ramucirumab is approved as subsequent systemic chemotherapies (in unselected patients) after platinum-based chemotherapy failure and is recommended by the NCCN [49]. Docetaxel is the cornerstone of second-line treatment in advanced NSCLC and has been the control arm in most randomized Phase 3 studies in this setting. Docetaxel monotherapy achieves an ORR of 5.5% to 14% with a median DOR of 5 to 6 months and median PFS of 2.8 to 4.2 months [24-26,33,35-39]. detailed data with docetaxel chemotherapy, or other chemotherapy combinations, are generally not available in patients whose NSCLC specifically harbors *EGFR Exon 20* insertion mutations. These features make it difficult to compare ORRs and its durability across studies with docetaxel to mobocertinib. Table 25 presents outcomes based on investigator assessment given that is what is reported with docetaxel, with similar assessments from Study 101.

Table 25: Summary of Outcomes With Docetaxel and Mobocertinib

	Docetaxel	Mobocertinib (N = 114)	
	Unselected	*EGFR Exon 20*	
		November 2020	May 2020
Investigator ORR, %	5.5 to 14 [a]	35.1	35.1
Investigator median DOR, months [b]	5.6 to 6.2	11.17	13.90
Investigator median PFS, months	2.8 to 4.2	7.33	7.29

Source: Study 101 Table 15.2.1D, 15.2.10D, and 15.2.12D. Data cutoff: 29 May 2020. Study 101 November 2020 Table 15.2.1D, 15.2.10D, and 15.2.12D. Data cutoff: 01 November 2020; and [24-26,33,35-39].

DOR: duration of response; KM: Kaplan-Meier; ORR: objective response rate; RECIST: Response Evaluation Criteria In Solid Tumors; PFS: progression-free survival.

[a] Per RECIST v1.1, in randomized studies where stable disease or progression are the primary endpoints, confirmation of response is not required.

[b] Follow-up duration differ between the studies.

Comparison between immunotherapy and mobocertinib

Table 26 presents outcomes based on investigator assessment given that is what is reported with PD-(L)1 inhibitors in the literature and in the meta-analysis. In the literature and in an meta-analysis, patients with NCSLC harboring an *EGFR Exon 20* insertion mutation treated with PD (L)1 inhibitors report a poor ORR and short PFS.

Table 26: Summary of Outcomes With PD-(L)1 Inhibitors and Mobocertinib in Patients With NSCLC Harboring EGFR Exon 20 Insertion Mutations

	PD-(L)1 Inhibitors (Meta-analysis) [a]	PD-(L)1 Inhibitors (Literature) [a]	Mobocertinib (N = 114)	
			November 2020	May 2020
Investigator ORR, %	3.5	0 to 19	35.1	35.1
Investigator median PFS, months	-	2 to 4 [b]	7.33	7.29

Source: Study 101 Table 15.2.1D, 15.2.10D, and 15.2.12D. Data cutoff: 29 May 2020. Study 101 November 2020 Table 15.2.1D, 15.2.10D, and 15.2.12D. Data cutoff: 01 November 2020; [48,50-54]; second-line immunotherapy white paper.

EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PD-(L)1: programmed cell death protein 1 or programmed death-ligand 1; ORR: objective response rate; PFS: progression-free survival.

[a] [48,50-54] and second-line immunotherapy white paper. The meta-analysis was conducted with only patients in the second-line or greater setting. Not all the literature references distinguish between first-line and second-line therapy.

[b] PFS was 1.7 and 2.3 months in 2 patients treated with monotherapy; PFS was 2.2, 6.6, and 8.7 months in 3 patients treated with combination therapy [50]. See other sources in the second-line immunotherapy white paper.

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Summary of RWD Analysis

Based on findings from multiple RWD sources, the currently available therapies (EGFR TKIs, chemotherapy, and immunotherapy) have limited clinical benefit to patients with *EGFR Exon 20* insertion mutations in a second-line setting or beyond, as well as concerns about adverse drug reactions and patient inconvenience. Therefore, these patients constitute a distinct, well-defined patient population with urgent unmet medical needs. Mobocertinib demonstrated clinically meaningful improvement, when compared to currently available therapies, for metastatic NSCLC patients with EGFR exon20 insertion mutations who have been previously treated with platinum chemotherapy.

The FDA's Assessment:

FDA acknowledges the Applicant's assessment of RWD but considers the RWD analyses to be exploratory.

8.1.3 Integrated Review of Effectiveness

Not applicable. There is one clinical study assessing effectiveness and the primary analysis data set is presented as requested in Section 8.1.2.1.6.

The FDA's Assessment:

FDA agrees.

8.1.4 Assessment of Efficacy Across Trials

Not applicable. There is one clinical study assessing efficacy.

The FDA's Assessment:

FDA agrees.

8.1.5 Integrated Assessment of Effectiveness

Not applicable. There is one clinical study assessing efficacy.

The FDA's Assessment:

Please refer to Section 8.1.2.1.10.

8.2 Review of Safety

The Applicant's Position:

The safety data in this Assessment Aid includes the Pooled Prior Platinum Safety Analysis Set, comprised of patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations who received 160 mg QD of mobocertinib and who had prior platinum chemotherapy treatment. This

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population provides the primary efficacy results to support the initial New Drug Application (NDA) submission in the United States:

- **Pooled Prior Platinum Analysis Set:** included patients (N = 114) from Study 101 (Part 1 [n = 6] + Expansion Cohort 1 of Part 2 [n = 22] + Part 3 [n = 86]) who have NSCLC with *EGFR Exon 20* insertion mutations, who had received prior treatment with platinum-based chemotherapy, and who received at least 1 dose of mobocertinib at 160 mg QD.

This Assessment Aid also includes 2 analysis populations for safety:

- **Mobocertinib 160 mg QD Analysis Population**: included all patients who received at least 1 dose of mobocertinib at 160 mg from Studies 101 (Parts 1, 2, and 3) and TAK-788-1003 (Part 1) (N = 256).
- **Overall Safety Analysis Population**: included all patients who received at least 1 dose of mobocertinib from Studies 101 (Parts 1, 2, and 3) and TAK-788-1003 (Part 1) (N = 325).

The safety data in the Module 2.7.4 and Integrated Summary of Safety for this application includes the Study 101 Part 3 Analysis Population rather than the Pooled Prior Platinum Analysis Set:

- **Study 101 Part 3 Analysis Population (dosed 160 mg QD)**: included all patients with previously treated NSCLC harboring *EGFR Exon 20* insertion mutations who received at least 1 dose of mobocertinib in this portion of the study (N = 96).

It should be noted that there is a significant overlap across the safety populations. For example, within the 325 patients in the Overall Safety Population, 256 patients are also included in the 160 mg QD Analysis Population; all patients in the Pooled Prior Platinum Analysis Set (n = 114) are included in both the Overall Safety Population and the 160 mg QD Analysis Population.

In Study 101 mobocertinib was continued unless the patient experienced progressive disease (PD) that required alternative therapy, intolerable toxicity, or met another discontinuation criterion. Mobocertinib treatment could continue after PD if, in the opinion of the investigator, the patient continued to experience clinical benefit.

Safety and tolerability were assessed by monitoring treatment-emergent adverse event (TEAEs), clinical laboratory evaluations, vital signs measurements, electrocardiograms (ECGs), physical examinations, pregnancy testing, and Eastern Cooperative Oncology Group (ECOG) performance status throughout treatment and for up to 30 days after the last dose of study drug.

<u>The FDA's Assessment:</u>

The FDA agrees with the Applicant's description of the three primary safety populations, including the pooled prior platinum analysis set (hereafter referred to as the **primary safety population**; n=114), mobocertinib 160 mg QD analysis population (hereafter referred to as the **pooled safety population**; n=256) and the overall safety analysis population (hereafter referred to as the **overall safety population**; n=325). FDA did not independently review the Study 101 Part 3 Analysis population (N=96), however this population accounted for 84% of the primary safety population.

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The FDA's analyses and assessment of safety are based on data from the May 29, 2020 data cut-off. Review of the 90-day safety update with a data cut-off date of November 1, 2020 did not reveal any new or worsening safety signals.

The safety population used to inform the Warnings and Precautions section (Section 5) of the USPI comprises 256 patients in the pooled safety population who received at least one dose of mobocertinib 160 mg daily. While patients in this population received at least one dose of mobocertinib 160 mg daily, approximately one-third of patients either started at a different dose (N=5) or had dose reductions (N=79) such that treatment-emergent adverse events may have occurred at doses other than 160 mg daily.

The population used to inform the Adverse Reactions section (Section 6) of the USPI includes the 114 patients in the primary safety population with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations who were previously treated with platinum-based chemotherapy and received mobocertinib 160 mg daily.

8.2.1 Safety Review Approach

The Applicant's Position:

The summary of safety includes information on study drug exposure; analyses of safety results including TEAEs and treatment-related adverse events (TRAEs); any TEAE Grade 3 or higher; on-study deaths; SAEs; AEs leading to dose interruption, dose reduction, or dose discontinuation; concomitant medications; AEs of clinical interest; clinical laboratory evaluations; and vital signs. In addition, this safety summary includes subgroup analyses for age (18 to <65 years; ≥65 years), sex (male; female), race (non-Asian; Asian), and region (North America + Europe; Asia).

The FDA's Assessment:

The FDA's approach to the safety review included evaluation of the clinical study report, case report forms, selected narratives, the Integrated Summary of Safety, and the original datasets submitted by the Applicant. 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 mobocertinib and additional analyses were performed for specific safety issues.

The FDA Grouped Terms (GT) used in this review are listed below:

- Diarrhea (GT): Diarrhea, Colitis, Enterocolitis
- Rash (GT): Rash, Dermatitis Acneiform, Rash Maculo-papular, Rash Pustular, Dermatitis, Urticaria, Acne, Rash Pruritic, Rash Papular, Vulvovaginal Rash, Rash Vesicular, Rash Erythematous, Rash Macular

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- Stomatitis (GT): Stomatitis, Mucosal Inflammation, Mouth Ulceration, Angular Chelitis, Cheilitis, Aphthous Ulcer, Tongue Ulceration, Glossitis, Oral Mucosal Eruption
- Fatigue (GT): Fatigue, Asthenia
- Musculoskeletal Pain (GT): Back Pain, Arthralgia, Neck Pain, Pain In Extremity, Musculoskeletal Chest Pain, Musculoskeletal Pain, Non-cardiac Chest Pain, Myalgia, Musculoskeletal Discomfort, Spinal Pain
- Dry Skin (GT): Dry Skin, Skin Atrophy, Xerosis
- Acute Kidney Injury (GT): Acute Kidney Injury, Glomerular Filtration Rate Decreased, Renal Impairment, Creatinine Renal Clearance Decreased, Renal Failure
- Paronychia (GT): Paronychia, Onychoclasis, Nail Disorder, Onycholysis, Onychalgia, Nail Infection, Onychomycosis, Onychomadesis, Nail Bed Tenderness, Nail Discoloration, Ingrowing Nail
- Dyspnea (GT): Dyspnea, Dyspnea Exertional
- Cough (GT): Cough, Productive Cough, Upper-airway Cough Syndrome
- Headache (GT): Headache, Head Discomfort
- Abdominal Pain (GT): Abdominal Pain, Abdominal Pain Upper, Abdominal Discomfort, Gastrointestinal Pain, Abdominal Tenderness
- Upper Respiratory Tract Infection (GT): Upper Respiratory Tract Infection, Nasopharyngitis, Rhinitis, Sinusitis, Respiratory Tract Infection, Sinus Disorder, Pharyngitis, Laryngitis
- Neuropathy Peripheral (GT): Neuropathy Peripheral, Paresthesia, Hypoesthesia, Peripheral Sensory Neuropathy, Hyperesthesia, Neuralgia, Peripheral Motor Neuropathy
- Hypertension (GT): Hypertension, Blood Pressure Increased
- Edema (GT): Edema Peripheral, Edema, Face Edema, Swelling, Periorbital Edema
- Dizziness (GT): Dizziness, Vertigo, Dizziness Postural
- Urinary Tract Infection (GT): Urinary Tract Infection, Cystitis, Escherichia Urinary Tract Infection
- Dysgeusia (GT): Dysgeusia, Ageusia
- Pneumonia (GT): Pneumonia, Pneumonia Aspiration, Pneumonia Bacterial
- QT prolongation (GT): Electrocardiogram QT Prolonged, Ventricular Arrhythmia
- Pleural Effusion (GT): Pleural Effusion, Malignant Pleural Effusion, Infectious Pleural Effusion
- Pneumonitis (GT): Pneumonitis, Interstitial Lung Disease

- Hypotension (GT): Hypotension, Orthostatic Hypotension
- Skin Infection (GT): Skin Infection, Cellulitis, Fungal Skin Infection
- Metastases To Central Nervous System (GT): Metastases To Central Nervous System, Metastases To Meninges
- Cardiac Failure (GT): Cardiac Failure, Ejection Fraction Decreased, Cardiac Failure Congestive, Cardiomyopathy, Stress Cardiomyopathy
- Cerebrovascular Accident (GT): Cerebrovascular Accident, Embolic Stroke, Thrombotic Stroke
- Brain Oedema (GT): Brain Edema, Vasogenic Cerebral Edema
- Ocular toxicity (GT): Dry Eye, Eye Pruritis, Abnormal Sensation in Eye, Eye Discharge, Blepharitis, Trichiasis, Conjunctival Hemorrhage, Vitreous Floaters, Blurred Vision and Corneal Edema

8.2.2 Review of the Safety Database

8.2.2.1 Overall Exposure

The Applicant's Position:

8.2.2.1.1 Disposition of Patients

Patient disposition was similar for each of the 3 safety populations (Table 27). Disease progression was the most common reason for study drug discontinuation within each of the 3 safety populations. Discontinuation due to an AE was comparable across these groups as well. Few patients within each of these groups discontinued treatment to begin treatment with another anti-cancer therapeutic.

Table 27: Patient Disposition (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
	Pooled Prior Platinum N = 114	**160 mg QD N = 256**	**Overall N = 325**
	n (%) of Patients		
Patients treated	114	256	325
Patients ongoing			
Ongoing on treatment	38 (33)	75 (29)	80 (25)
Ongoing on study	70 (61)	-	-
Reason for discontinuing study drug[a]	76 (67)	181 (71)	245 (75)
Adverse Event	14 (18)	28 (11)	38 (12)
Protocol violation	0	0	0
Lost to follow-up	0	0	0

Table 27: Patient Disposition (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
	Pooled Prior Platinum N = 114	160 mg QD N = 256	Overall N = 325
	n (%) of Patients		
Withdrawal by patient	8 (11)	15 (6)	23 (7)
Study terminated by sponsor	0	-	-
Pregnancy	0	0	0
Entry into another therapeutic clinical study/start a new anti-cancer therapy	2 (3)	2 (<1)	2 (<1)
Symptomatic deterioration	0	0	1 (<1)
Clinical Progressive Disease	25 (33)	82 (32)	123 (38)
Progressive Disease (RECIST 1.1)	24 (32)	28 (11)	28 (9)
Other	3 (4)	26 (10)	30 (9)
Discontinued the study[b]	44 (39)	117 (46)	176 (54)
Death	30 (68)	71 (28)	114 (35)
Adverse Event	2 (5)	2 (<1)	2 (<1)
Protocol deviation	0	0	0
Lost to follow-up	2 (5)	2 (<1)	2 (<1)
Withdrawal by patient	6 (14)	17 (7)	28 (9)
Completed	-	9 (4)	12 (4)
Other	4 (9)	16 (6)	18 (6)
Time on study (months)[c]			
n	114	-	-
Mean (SD)	10.60 (6.560)	-	-
Median	8.76	-	-
Minimum, maximum	1.2, 31.2	-	-

Source: Module 2.7.4 Table 18.1.1.1.2, Table 15.1.3D. Data cutoff: 29 May 2020.
QD: once daily; RECIST: Response Evaluation Criteria in Solid Tumors; SD = standard deviation.
[a] Subcategory percentages are based on the number of patients who discontinued study drug.
[b] Subcategory percentages are based on the number of patients who discontinued study.
[c] Time on study is calculated as [(last visit date - enrollment date) +1]/30.4375.

8.2.2.1.2 Exposure

Overall median time on treatment for the Pooled Prior Platinum Population was 6.97 months, which was consistent with both the 160 mg QD Population (5.62 months) and the Overall Population (5.22 months), as outlined in Table 28. Relative median dose intensity was 100% for the Pooled Prior Platinum Population; and was also 100% in the 160 mg QD Population and the Overall Population.

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Table 28: Patient Study Drug Exposure (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
	Pooled Prior Platinum N = 114	**160 mg QD N = 256**	**Overall N = 325**
Time on study treatment (months) [a]			
Mean (SD)	7.56 (5.766)	6.57 (5.429)	6.29 (5.811)
Median	6.97	5.62	5.22
Minimum, maximum	0.0, 30.9	0, 30.9	0, 35.4
Duration of exposure, n (%)			
<1 month	8 (7)	26 (10)	45 (14)
1 to <3 months	17 (15)	47 (18)	65 (20)
3 to <6 months	21 (18)	61 (24)	76 (23)
6 to <12 months	52 (46)	92 (36)	100 (31)
≥12 months	16 (14)	30 (12)	39 (12)
Number of days dosed			
Mean (SD)	220.2 (173.09)	189.9 (162.24)	182.1 (173.77)
Median	198.5	163.0	137.0
Minimum, maximum	1, 927	1, 927	1, 1060
Mobocertinib cumulative dose (mg)			
Mean (SD)	32,638.6 (26,328.42)	27,012.5 (23,449.57)	24,406.7 (23,919.43)
Median	28,060.0	22,540.0	17,760.0
Minimum, maximum	160, 148320	160, 148,320	65, 148,320
Mobocertinib dose intensity (mg/day) [b]			
Mean (SD)	139.08 (27.608)	134.60 (29.650)	122.49 (40.511)
Median	156.65	150.32	125.49
Minimum, maximum	64.6, 160.0	45.2, 160.0	4.0, 180.0
Mobocertinib relative dose intensity (%) [c]			
Mean (SD)	92.31 (12.283)	92.33 (20.891)	93.52 (19.923)
Median	100.0	100.00	100.00
Minimum, maximum	51.2, 100.0	35.8, 285.1	35.8, 285.1
Total person years		-	-
Mean (SD)	0.63 (0.480)	-	-
Median	0.58	-	-
Minimum, maximum	0.0, 2.6	-	-

Source: Module 2.7.4 Table 18.1.1.5.1, Table 15.1.17D. Data cutoff: 29 May 2020.

QD: once daily; SD: standard deviation.

[a] Time (months) on study treatment = (last non-zero dose date – first dose date + 1)/30.4375.

[b] Dose intensity = total cumulative dose/time (days) on study treatment.

[c] Relative dose intensity = total cumulative dose administered/total dose planned × 100%, where the total dose planned does not consider intrapatient dose-escalation.

Table 28: Patient Study Drug Exposure (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
	Pooled Prior Platinum N = 114	**160 mg QD N = 256**	**Overall N = 325**

[d] Total person years = Time (days) on study treatment/365.25. The total person years in an analysis population will be the sum of the total person years of all the patients in this population.

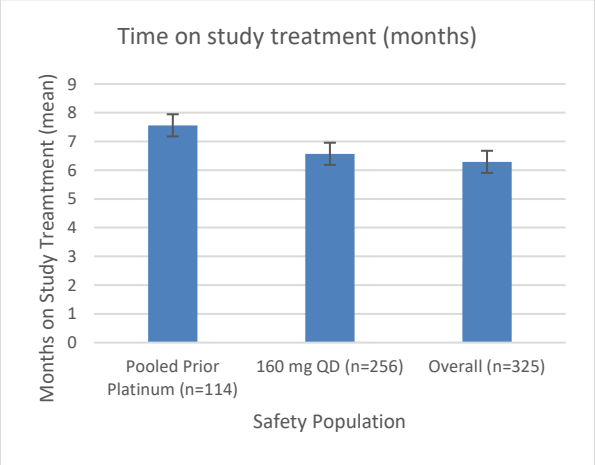
The FDA's Assessment:

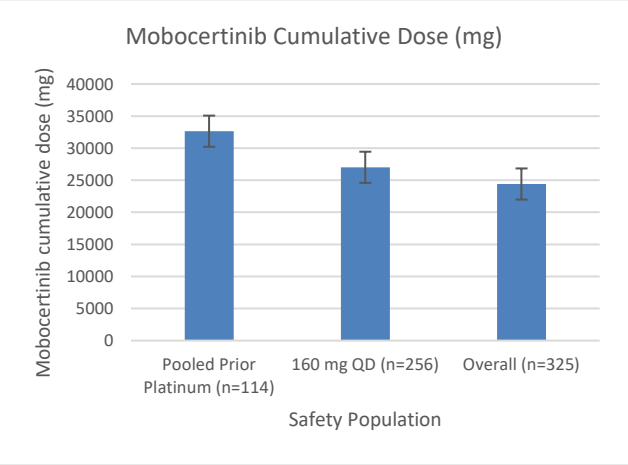
The FDA agrees with the Applicant's description of patient disposition. Most treatment discontinuations were due to progressive disease and the most common reason for study discontinuation was death. Of the 30 patients in the overall safety population who discontinued mobocertinib due to "Other" reasons, 10 discontinued due to death, 13 due to "physician decision" and 7 were not reported.

As of the data cut-off of May 29, 2020, the median time on study treatment for the 256 patients in the pooled safety population was 5.62 months, ranging from 0 to 30.9 months, and 29% of patients were still receiving treatment.

While drug exposure was generally similar across the safety populations, patients in the primary safety population (n=114) had the longest period of time on study treatment as well as the largest mobocertinib cumulative dose. Most patients (64%) received study treatment for 3 to 12 months and 14% received study treatment for longer than 12 months.

Table 29: Time on study treatment and cumulative dose (FDA table)





Reference ID: 4857343

8.2.2.2 Relevant Characteristics of the Safety Population

The Applicant's Position:

The general demographic characteristics for Pooled Prior Platinum Safety Population aligned with both the 160 mg QD Population and the Overall Population, as outlined in Table 30.Most patients in each population were female, aged 50 to 64 years, with a median age of 60.0 to 61.0 across the 3 safety populations.

Table 30: Demographic Characteristics (All Analysis Populations; Data Cutoff 29 May 2020)

	Pooled Prior Platinum N = 114	160 mg QD N = 256	Overall N = 325
Age (years)			
Mean (SD)	59.6 (11.53)	60.4 (11.16)	60.6 (11.22)
Median	60.0	61.0	61.0
Min, max	27, 84	24, 86	24, 86
Age categories, n (%)			
18-44 years	10 (8.8)	-	-
45-59 years	46 (40.4)	-	-
60-74 years	50 (43.9)	-	-
≥75 years	8 (7.0)	-	-
18-49 years	20 (17.5)	45 (18)	55 (17)
50-64 years	52 (45.6)	115 (45)	142 (44)
65-74 years	34 (29.8)	72 (28)	99 (30)
75-84 years	8 (7.0)	22 (9)	27 (8)
≥85 years	0	2 (<1)	2 (<1)
Gender, n (%)			
Male	39 (34.2)	87 (34)	106 (33)
Female	75 (65.8)	169 (66)	219 (67)
Ethnicity, n (%)			
Hispanic or Latino	1 (0.9)	12 (5)	16 (5)
Not Hispanic and Latino	113 (99.1)	231 (90)	289 (89)
Not Reported	0	13 (5)	20 (6)

Reference ID: 4857343

Table 30: Demographic Characteristics (All Analysis Populations; Data Cutoff 29 May 2020)

	Pooled Prior Platinum N = 114	160 mg QD N = 256	Overall N = 325
Race, n (%)			
Asian	68 (59.6)	102 (40)	119 (37)
Asian Indian	2 (1.8)	2 (<1)	2 (<1)
Chinese	42 (36.8)	52 (20)	56 (17)
Japanese	6 (5.3)	20 (8)	28 (9)
Korean	14 (12.3)	15 (6)	15 (5)
Other	1 (0.9)	9 (4)	12 (4)
Not reported	3 (2.6)	4 (2)	6 (2)
Black or African American	3 (2.6)	12 (5)	16 (5)
White	42 (36.8)	139 (54)	182 (56)
Other	0	0	3 (<1)
Not reported	1 (0.9)	3 (1)	5 (2)
Geographic region, n (%)			
Asia Pacific (China, Japan, other)	55 (48.2)	70 (27)	77 (24)
Europe	6 (5.3)	10 (4)	10 (3)
North America	53 (46.5)	176 (69)	238 (73)

Source: Module 2.7.4 Table 18.1.1.2.1, 18.1.1.2.2, Table 15.1.7D, Table 15.1.8D. Data cutoff: 29 May 2020.
QD: once daily. SD: standard deviation.

Key baseline characteristics for the Pooled Prior Platinum Safety Population were consistent with both the 160 mg QD and Overall Populations. Most patients in the Pooled Prior Platinum Safety Population had Stage IV adenocarcinoma at the time of study entry, with the lung as the most common site of disease, as outlined in Table 31. These demographics are consistent with the 160 mg QD Population, and the Overall Study Population. Brain and bone were other common sites of disease involvement across the 3 study populations, as was also a baseline ECOG score of 1. Most patients across the 3 safety populations had no prior smoking history.

Table 31: Baseline Characteristics (All Analysis Populations; Data Cutoff 29 May 2020)

	Pooled Prior Platinum N = 114	160 mg QD N = 256	Overall N = 325
Time since initial diagnosis (months)			
Mean (SD)	23.80 (27.915)	26.33 (30.948)	26.30 (30.022)
Median	14.72	16.18	16.59
Min, max	1.1, 161.8	0.8, 259.2	0.8, 259.2

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Table 31: Baseline Characteristics (All Analysis Populations; Data Cutoff 29 May 2020)

	Pooled Prior Platinum N = 114	160 mg QD N = 256	Overall N = 325
Stage at study entry, n (%)			
IIIA	0	0	1 (<1)
IIIB	1 (0.9)	3 (1)	3 (<1)
IV	113 (99.1)	244 (95)	307 (94)
Missing	0	9	14
Histopathological classification of NSCLC at study entry, n (%)			
Adenocarcinoma	112 (98.2)	245 (96)	311 (96)
Adenosquamous carcinoma	0	1 (<1)	2 (<1)
Large cell	1 (0.9)	2 (<1)	2 (<1)
Squamous	1 (0.9)	4 (2)	5 (2)
Other	0	4 (2)	5 (2)
Site involvement at study entry, n (%)			
Brain	40 (35.1)	102 (40)	142 (44)
Bone	47 (41.2)	117 (46)	155 (48)
Liver	24 (21.1)	55 (21)	76 (23)
Lung	110 (96.5)	231 (90)	292 (90)
Other	93 (81.6)	202 (79)	256 (79)
Smoking status as of informed consent, n (%)			
Never	81 (71.1)	167 (65)	219 (67)
Current	2 (1.8)	3 (1)	3 (<1)
Former	31 (27.2)	85 (33)	102 (31)
Unknown	0	1 (<1)	1 (<1)
ECOG performance status, n (%)			
0	29 (25.4)	82 (32)	95 (29)
1	85 (74.6)	174 (68)	230 (71)

Source: Module 2.7.4 Table 18.1.1.2.2, Table 15.1.8D. Data cutoff: 29 May 2020.
ECOG: Eastern Cooperative Oncology Group; NSCLC: non-small cell lung cancer; QD: once daily.
Baseline values are the last valid values observed prior to first exposure to study drug.

The FDA's Assessment:

The FDA agrees with the Applicant's presentation of the demographic and baseline characteristics of the safety populations from Study 101. The median age of patients in the pooled safety population was 61 years old; 24 of 256 (9%) patients were 75 years or older. The higher incidence of females versus males (66% vs. 34%, respectively) is consistent with the known higher incidence of EGFR exon 20 insertion mutations in females.

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Approximately 40% of patients were Asian in the pooled safety population, compared to 60% in the primary safety population; this is likely due to the location of the dose escalation studies (primarily in the United States), whereas the dose expansion portions of the study enrolled patients internationally, including multiple sites in Asia. In the pooled safety population, 96% of patients had adenocarcinoma histology and 95% were Stage IV at study entry. Metastatic site involvement at study entry included brain (40%), bone (46%), liver (21%) and other sites (79%). Approximately two-thirds of patients were never smokers, and all had ECOG performance status of 0 to 1.

8.2.2.3 Adequacy of the Safety Database

The Applicant's Position:

The population recruited in Study 101 (patients with NSCLC harboring *EGFR Exon 20* insertion mutations) adequately represents the target population for the proposed indication. Demographic, disease, and other baseline characteristics in Pooled Prior Platinum Population Analysis Set were representative of the intended patient population for the proposed indication.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position on the adequacy of the safety database. However, while age and sex are representative of the intended population, the enrollment of 1% Hispanic or Latino and 3% Black patients in the primary safety population is lower than would be expected for the US population (Choudhury, 2021). The Applicant will conduct an analysis containing data from clinical trials enrolling a sufficient representation of U.S. racial and ethnic subpopulations, including Black or African American patients, to further characterize the safety and efficacy of mobocertinib in Black or African American patients with EGFR exon 20 insertion mutated NSCLC.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

8.2.3.1 Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

This submission was of adequate quality for clinical review. Each study was conducted within GCP. There are no concerns regarding the integrity of the submission.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a complete review of the safety of mobocertinib. FDA issued several information requests during the review cycle to obtain clarification and additional information regarding safety data included in the NDA and all requests were addressed appropriately.

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8.2.3.2 Categorization of Adverse Event

The Applicant's Position:

AEs were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that may or may not have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a preexisting condition that occurs after informed consent is also an AE.

- **Related AE**: Related AE is defined as 1 in which there is a reasonable causal relationship between the study drug or the treatment regimen and the AE, as determined by the investigator.
- **TEAEs**: TEAE is defined as any AE that occurs time from first dose of study drug and through the end of treatment until 30 days after the last dose of study drug. Assessment was done by the investigator.
- **SAE**: An AE is considered an *SAE* if at least 1 of the following conditions applies: death; life-threatening AE; results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; inpatient hospitalization or prolongation of existing hospitalization; a congenital anomaly/birth defect; occurrence or diagnosis of a new cancer that is histopathologically different from the cancer under study; and an important medical event.
- **On-study deaths** An on study death is defined as a death that occur between the first dose of study drug and within 30 days after the last dose of study drug.

The FDA's Assessment:

The FDA agrees with the Applicant's categorization of adverse events (AEs) for Study 101 and Study TAK-788-1003. AEs were coded using MedDRA version 23.0 and were graded according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0). The safety assessment focused on the frequency and severity of all treatment-emergent AEs (TEAEs), which were defined as AEs occurring after the first dose of study treatment to within 30 days after the last dose of study therapy. Additional analyses included assessment of TEAEs leading to death, serious adverse events (SAEs), and TEAEs leading to dose reduction, interruption, or permanent discontinuation of mobocertinib. The FDA review was completed using MedDRA preferred terms (PTs) and CTCAE grade as well as custom grouped terms (GTs) when performing independent analyses of AEs (see Section 8.2.1 for a description of FDA's custom GTs).

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8.2.3.3 Routine Clinical Tests

The Applicant's Position:

To support this application the following safety measures for routine clinical tests for safety surveillance for the 3 safety analysis populations were used:

- **Hematology**: Results and change from baseline over time; results based on NCI-CTCAE grade; incidence of clinically significant laboratory abnormality by NCI-CTCAE grade;
- **Chemistry**: Results and change from baseline over time; results based on NCI-CTCAE grade; incidence of clinically significant laboratory abnormality by NCI-CTCAE grade Vital signs included temperature, pulse, respiratory rate, and seated blood pressure;
- **Potentially clinically significant laboratory abnormalities**: Incidence of potentially clinically significant laboratory abnormalities by NCI-CTCAE grade;

No integrated analyses of vital signs have been performed for the summary of safety. Vital sign results are presented in the individual CSRs.

No integrated analyses of ECGs have been performed for the summary of safety. ECG results are presented in the individual study CSRs.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the clinical safety monitoring for Study 101. Echocardiograms were not performed routinely during the conduct of Study 101, but were obtained as part of a work-up for symptoms of cardiac failure.

8.2.4 Safety Results

8.2.4.1 Deaths

The Applicant's Position:

On-study deaths occurred in 11% of the Pooled Prior Platinum Population, which is similar to the number of on-study deaths in the 160 mg QD Population (11%) and the Overall Population (13%), as outlined in Table 32. Deaths related to the study drug occurred in ≤1% of patients across the 3 safety populations, including deaths due to respiratory failure, pneumonitis, and cardiac failure. Remaining on-study deaths were not related to study drug but related to the underlying disease (ie, neoplasm progression and NSCLC).

Of the 12 on-study deaths (11%) in the Pooled Prior Platinum Population 10 of the 12 deaths were associated with the underlying disease and were not related to the study drug; the 2 additional deaths, both noted in Part 3 of Study 101, were 1 death due to multiple organ failure not related to study drug, and 1 death due to worsening cardiac failure which was deemed related to study drug.

The majority of the deaths in the Overall Safety Population that occurred greater than 30 days after the last dose of study drug were reported as disease progression.

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Table 32: Summary of On-Study Deaths (All Analysis Populations; Data Cutoff 29 May 2020)

	All On-Study Death			Drug-Related			Drug Not Related		
Cause of Death	Pooled Prior Platinum N=114 n (%)	160 mg QD N=256 n (%)	Overall Safety N=325 n (%)	Pooled Prior Platinum N=114 n (%)	160 mg QD N=256 n (%)	Overall Safety N=325 n (%)	Pooled Prior Platinum N=114 n (%)	160 mg QD N=256 n (%)	Overall Safety N=325 n (%)
All On-study Deaths	12 (11)	27 (11)	41 (13)	1 (<1)	2 (<1)	3 (<1)	11 (10)	25 (10)	38 (12)
Neoplasm progression	1 (<1)	2 (<1)	7 (2)	0	0	0	1 (<1)	2 (<1)	7 (2)
Non-small cell lung cancer	2 (2)	4 (2)	6 (2)	0	0	0	2 (2)	4 (2)	6 (2)
Respiratory failure	1 (<1)	3 (1)	5 (2)	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)	4 (1)
Pneumonia	0	3 (1)	4 (1)	0	0	0	0	3 (1)	4 (1)
Disease progression	2 (2)	2 (<1)	2 (<1)	0	0	0	2 (2)	2 (<1)	2 (<1)
Metastases to central nervous system	1 (<1)	2 (<1)	2 (<1)	0	0	0	1 (<1)	2 (<1)	2 (<1)
Metastases to meninges	1 (<1)	2 (<1)	2 (<1)	0	0	0	1 (<1)	2 (<1)	2 (<1)
Multiple organ dysfunction syndrome	1 (<1)	2 (<1)	2 (<1)	0	0	0	1 (<1)	2 (<1)	2 (<1)
Cardiac arrest	0	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)
Cardiac failure	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	0	0
Cerebrovascular accident	0	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)
Depressed level of consciousness	0	0	1 (<1)	0	0	0	0	0	1 (<1)
Dyspnoea	1 (<1)	1 (<1)	1 (<1)	0	0	0	1 (<1)	1 (<1)	1 (<1)
Hypoxia	1 (<1)	1 (<1)	1 (<1)	0	0	0	1 (<1)	1 (<1)	1 (<1)
Lung cancer metastatic	0	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)
Lung neoplasm malignant	0	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)
Malignant ascites	0	0	1 (<1)	0	0	0	0	0	1 (<1)

Table 32: Summary of On-Study Deaths (All Analysis Populations; Data Cutoff 29 May 2020)

	All On-Study Death			Drug-Related			Drug Not Related		
Cause of Death	Pooled Prior Platinum N=114 n (%)	160 mg QD N=256 n (%)	Overall Safety N=325 n (%)	Pooled Prior Platinum N=114 n (%)	160 mg QD N=256 n (%)	Overall Safety N=325 n (%)	Pooled Prior Platinum N=114 n (%)	160 mg QD N=256 n (%)	Overall Safety N=325 n (%)
Malignant pleural effusion	0	0	1 (<1)	0	0	0	0	0	1 (<1)
Non-small cell lung cancer Stage IV	1 (<1)	1 (<1)	1 (<1)	0	0	0	1 (<1)	1 (<1)	1 (<1)
Pneumonitis	0	0	1 (<1)	0	0	1 (<1)	0	0	0

Source: Module 2.7.4 Table 18.1.1.17.1. Data cutoff: 29 May 2020.

QD: once daily.

Note: A patient reporting the same event more than once has that event counted only once within each preferred term. On-study deaths are defined as deaths that occur between the first dose of study drug and within 30 days after the last dose of study.

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The FDA's Assessment:

Fatal TEAEs occurred in 11-13% of patients across the three safety populations. FDA reviewed all 41 fatal adverse events that occurred in the overall safety population (n=325) as of the data cut-off of May 29, 2020.

In the pooled safety population (n=256), there were 27 fatal TEAEs. Fourteen patients (52%) died due to disease progression (preferred terms included neoplasm progression, non-small cell lung cancer, disease progression, metastases to central nervous system/meninges, lung cancer metastatic, lung neoplasm malignant). The remaining 13 deaths (48%) were attributed to the following causes other than disease progression: respiratory failure (n=3), pneumonia (n=3), dyspnea (n=1), hypoxia (n=1), multiple organ dysfunction syndrome (n=2), cardiac failure (n=1), cardiac arrest (n=1) and cerebrovascular accident (n=1). Based on review of the patient narratives, the fatal AEs which for which attribution to mobocertinib could not be ruled out included three cases of respiratory failure and one case of cardiac failure, as described in Table 33 below.

In the overall safety population (n=325), there were 14 additional deaths. Of these, 9 were attributed to disease progression. Based on review of the patient narratives for the remaining 5 deaths, four were attributable to infection or disease progression (preferred terms included respiratory failure [n=2], pneumonia [n=1], and depressed level of consciousness [n=1]. Finally, there was one fatal case of pneumonitis referred to by the Applicant in Section 8.4.2.1, Subject AP32788-15-[redacted] (b) (6) was in the overall safety population (n=325) but not the mobocertinib once daily population (n=256); therefore, this event was not included in the description of fatal and pneumonitis adverse reactions in the USPI.

In addition to the 41 patients with fatal TEAEs, there were 6 non-treatment emergent deaths in the overall safety population that occurred beyond 30 days (range 32 to 157 days) after the last dose of study drug. These events included one case each of respiratory failure, subdural hemorrhage, pneumonia, dyspnea, disease progression and renal failure. The case of renal failure was in the setting of incomplete intestinal obstruction and abdominal metastases that occurred 32 days after mobocertinib was discontinued due to disease progression; the event of renal failure was attributed as possibly related to mobocertinib (further detailed in Section 8.2.4.5).

In the primary safety population (n=114), fatal adverse reactions occurred in 2 (1.8%) patients, including one event each of cardiac failure and pneumonitis, both of which are described in product labeling.

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Table 33 describes the fatal treatment-emergent AEs and FDA's assessment of the causality in greater detail.

Table 33: FDA Assessment of Causality for Treatment-Emergent Fatal Adverse Events Not Clearly Attributable to Disease Progression in Pooled Safety Population (N=256) (FDA table)

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
AP32788-15-(b) (6)	64-year-old female taking mobocertinib 160 mg daily developed grade 2 diarrhea four days after starting mobocertinib and the dose was reduced to 120 mg daily. Approximately two months after starting study treatment she developed shortness of breath, cough and hypoxia requiring hospitalization. Chest CT showed increased bilateral pleural effusions and new upper lobe predominant ground glass opacities with clinical concern for pneumonitis versus infection. Respiratory virus panel was positive for coronavirus (prior to COVID19 pandemic) and metapneumovirus. She required escalating supportive care, was ultimately discharged home and died the next day due to **hypoxemic respiratory failure**, thirteen days after admission.	Pneumonitis While the patient's death was likely multifactorial, in part due to metapneumovirus and coronavirus, the patient's symptoms and the presence of ground glass opacities on CT imaging are also consistent with drug-indued pneumonitis. Therefore, FDA was unable to rule out whether mobocertinib contributed to the event of hypoxemic respiratory failure.	Yes
AP32788-15-(b) (6)	65-year-old male taking mobocertinib 160 mg daily developed shortness of breath, fatigue, back pain, cough and chest congestion approximately 1.5 months after starting mobocertinib. He was hospitalized and chest CT showed extensive bilateral ground glass opacities, and subsequently treated with antibiotics for possible pneumonia as well as methylprednisolone for possible pneumonitis. He died due to **respiratory failure** one month after admission.	Pneumonitis While the patient's death was likely multifactorial, the patient's symptoms, CT imaging, and the use of corticosteroids as part of his management, are consistent with pneumonitis, for which the contribution of mobocertinib cannot be ruled out.	Yes
TAK78801-788101-(b) (6)	53-year-old male taking mobocertinib 160 mg daily developed shortness of breath and cough approximately 8.5	Pneumonitis While the patient's death was	Yes

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Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
	months after starting mobocertinib. He was hospitalized and chest CT showed extensive ground glass opacities in the left lung and worsening metastatic disease. Despite high dose steroid therapy and broad-spectrum antibiotics, he had progressive worsening respiratory status and ground glass opacification of the lungs. He died due to **hypoxic respiratory failure** three days after admission.	likely multifactorial, the patient's symptoms, CT imaging, and the use of corticosteroids as part of his management, are consistent with pneumonitis, for which the contribution of mobocertinib cannot be ruled out	
AP32788-15-(b) (6)	61-year-old female taking mobocertinib 160 mg daily was hospitalized due to hypoxia approximately 4.5 months after starting mobocertinib. Chest CT showed bilateral pulmonary infiltrates with an increased focal consolidation in the left lung, clinically consistent with infectious **pneumonia**. She received antibiotics and steroids while admitted and ultimately died due to pneumonia nine days after admission.	Pneumonia FDA considers infectious pneumonia most likely given the description of imaging and treatment with antibiotics.	No
AP32788-15-(b) (6)	64-year-old female was initially taking mobocertinib 160 mg daily, decreased to 120 mg daily after one month of therapy due to gastroesophageal reflux disease. Nearly four months after starting therapy, she was hospitalized with cough, shortness of breath and pleuritic chest pain and found to have leukocytosis and multifocal pulmonary opacities with pleural effusions. diagnosed with pneumonia. She required escalating supportive care, was transitioned to comfort care and died due to **pneumonia** five days after admission.	Pneumonia FDA considers infectious pneumonia most likely given the description of leukocytosis and imaging.	No
AP32788-15-(b) (6)	66-year-old female taking mobocertinib 160 mg daily for one day developed paresthesias; a brain MRI showed acute to subacute multifocal ischemic infarcts consistent with a cardioembolic stroke and she was started on apixaban. Two weeks after starting treatment she	Pneumonia Given the history of the patient's recent hospitalization, imaging and treatment with antibiotics, FDA considers this to be most likely an event of	No

Reference ID: 4857343

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
	developed diarrhea, weakness and fatigue. Chest CT showed infiltrates increasing in the right lung base since previous exam. She was diagnosed with a lung infection, hospitalized and treated with antibiotics. She died due to **lung infection** two weeks after admission.	infectious pneumonia and unlikely to be due to mobocertinib.	
TAK78801-788101- (b) (6)	67-year-old female taking mobocertinib 160 mg daily for approximately 6 months developed shortness of breath which was clinically attributed to disease progression in the context of prior imaging (no repeat imaging was done at the onset of this AE). Treatment was interrupted and she died three days later due to **dyspnea**.	Dyspnea Determination of causality is difficult in this case due to limited information and no imaging, however given the history disease progression is most likely.	No
AP32788-15-101- (b) (6)	59-year-old male initially taking mobocertinib 160 mg daily developed Grade 1 diarrhea one week after starting treatment and the dose was reduced to 120 mg daily. Approximately 2.5 months after starting treatment, he developed shortness of breath and was hospitalized. Chest CT showed a right partially loculated pleural effusion, thoracentesis was performed and confirmed malignant pleural effusion. He was discharged then readmitted two weeks later due to worsening shortness of breath and found to have pulmonary embolism. He was discharged to home hospice and died two days later due to **hypoxia.**	Disease progression Given the patient's known malignant pleural effusion and enrollment in hospice, FDA determined that this patient's death was most likely a consequence of lung cancer progression. FDA considers this event unlikely to be due to mobocertinib.	No
AP32788-15-101 (b) (6)	60-year-old female initially taking mobocertinib 160 mg daily on treatment for approximately 1 month, stopped mobocertinib due to unclear reasons and 15 days later was hospitalized for to worsening respiratory distress and hypotension. Chest CT showed pleural and pericardial effusions requiring drainage. Despite escalating care, she developed worsening hypoxic	Disease progression Given the patient's known metastatic disease with pleural and pericardial effusions, FDA determined that this patient's death was most likely a consequence of lung cancer progression. FDA considers this event unlikely to be due to	No

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Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
	respiratory failure, shifted to comfort care and died due to **multi-system organ failure** (heart, respiratory, kidney, acidosis) 3 days after admission.	mobocertinib.	
TAK78801-788101- (b) (6)	68-year-old male taking mobocertinib 160 mg daily developed dyspnea and dizziness approximately one month after starting mobocertinib and was hospitalized for pleural and pericardial effusions. The patient declined pericardial drainage, transitioned to comfort care, and subsequently died at home due to **multi-organ failure** 4 days after admission.	Disease progression Given the patient's known metastatic disease with pleural and pericardial effusions, FDA determined that this patient's death was most likely a consequence of lung cancer progression. FDA considers this event unlikely to be due to mobocertinib.	No
TAK78801-788101- (b) (6)	68-year-old male taking mobocertinib 160 mg daily developed shortness of breath approximately 3 months after starting mobocertinib. He was hospitalized and found to have a decreased left ventricular ejection fraction (LVEF 20%) with borderline LV dilation, mild mitral regurgitation/pulmonary hypertension with elevated serum troponin. He was diagnosed with non-ischemic cardiomyopathy with negative viral studies, and despite escalating supportive care he died of **worsening heart failure** 7 days after admission.	Cardiac failure While the patient's death was likely multifactorial, FDA was unable to rule out whether mobocertinib caused or contributed to possible cardiac failure given the acute decompensation, significantly decreased ejection fraction compared to his normal baseline, and no other apparent etiology.	Yes
AP32788-15-101- (b) (6)	63-year-old female initially taking mobocertinib 160 mg daily on treatment for approximately 6 months, stopped mobocertinib due to progressive disease. Eighteen days after stopping mobocertinib and ten days after starting new anti-cancer therapy (carboplatin, pemetrexed and pembrolizumab), she was found pulseless at home by a family member. She was resuscitated and hospitalized, but despite escalating supportive care she died 1 day after admission due to the **cardiac arrest**.	Cardiac arrest Given the patient's known metastatic disease and clinical history, this event is likely secondary to cardiac arrest in the setting of disease progression. FDA considers this event unlikely to be due to mobocertinib.	No

Reference ID: 4857343

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
AP32788-15-101 (b) (6)	70-year-old female taking mobocertinib 160 mg daily for approximately 3 weeks developed acute right-sided weakness and aphasia. She was admitted and MRI showed a left temporal **ischemic stroke** and bilateral deep vein thromboses were found. Despite escalating supportive care, she developed worsening cardiac and renal function, shifted to comfort care and died 6 days after admission.	Disease progression While the patient's death was likely multifactorial, hypercoagulability from the underlying malignancy likely led to bilateral venous thromboses which led to ischemic stroke and multi-organ dysfunction.	No

8.2.4.2 Serious Adverse Events

The Applicant's Position:

In the Pooled Prior Platinum Population, SAEs were reported for 52 patients (46%). The most common SAEs (in ≥5% of patients) in this study population included diarrhoea (8%) and Dyspnoea (7%). The number of SAEs in the Pooled Prior Platinum Population is consistent with the number of SAEs in the 160 mg QD Population (41%) and the Overall Population (43%), as outlined in Table 34. The most common treatment-emergent SAEs (ie, dyspnoea and diarrhoea) were consistent across the 3 safety populations.

Table 34: Most Common (Reported in ≥2% of Patients in Any Group) Treatment-Emergent SAEs by SOC and PT (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
	Pooled Prior Platinum	160 mg QD	Overall
SOC	N=114	N = 256	N = 325
PT	n (%) of Patients		
Patients with any treatment-emergent SAE	**52 (46)**	**105 (41)**	**140 (43)**
Respiratory, thoracic, and mediastinal disorders	**11 (10)**	**27 (11)**	**38 (12)**
Dyspnoea	8 (7)	16 (6)	21 (6)
Respiratory failure	1 (<1)	4 (2)	7 (2)
Gastrointestinal disorders	**17 (15)**	**28 (11)**	**36 (11)**
Diarrhoea	9 (8)	13 (5)	15 (5)
Vomiting	5 (4)	11 (4)	13 (4)
Nausea	3 (3)	5 (2)	7 (2)

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Table 34: Most Common (Reported in ≥2% of Patients in Any Group) Treatment-Emergent SAEs by SOC and PT (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
	Pooled Prior Platinum	160 mg QD	Overall
SOC	N=114	N = 256	N = 325
PT	n (%) of Patients		
Infections and infestations	**7 (6)**	**21 (8)**	**30 (9)**
Pneumonia	1 (<1)	10 (4)	15 (5)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**7 (6)**	**15 (6)**	**25 (8)**
Neoplasm progression	1 (<1)	3 (1)	8 (2)
General disorders and administration site conditions	**9 (8)**	**14 (5)**	**14 (4)**
Pyrexia	4 (4)	5 (2)	5 (2)
Metabolism and nutrition disorders	**3 (3)**	**9 (4)**	**14 (4)**
Dehydration	2 (2)	5 (2)	9 (3)
Renal and urinary disorders	**4 (4)**	**10 (4)**	**10 (3)**
Acute kidney injury	2 (2)	8 (3)	8 (2)

Source: Module 2.7.4 Table 18.1.1.13.5. Data cutoff: 29 May 2020.

PT: Preferred Term; QD: once daily; SAE: serious adverse event; SOC: System Organ Class.

Note: Treatment-emergent adverse events (TEAEs) are defined as any adverse event that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug. A patient reporting the same event more than once has that event counted only once within each system organ class, and once within each preferred term. MedDRA Dictionary (Version 23.0) was used for coding adverse events.

Treatment-related SAEs occurred in 18% of the Pooled Prior Platinum Population, which is consistent with the number of events in the 160 mg QD Population (16%) and the Overall Population (15%), as outlined in Table 35. The most common treatment-related SAEs (in ≥2% of patients) included diarrhoea, vomiting, and nausea, which were consistent across the 3 safety populations.

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Table 35: Most Common (Reported in ≥2% of Patients in Any Group) Treatment-Related SAEs by SOC and PT (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
	n (%) of Patients		
SOC	Pooled Prior Platinum N=114	160 mg QD N = 256	Overall N = 325
PT	n (%) of Patients		
Patients with any treatment-related SAE	**21 (18)**	**40 (16)**	**49 (15)**
Gastrointestinal disorders	**12 (11)**	**20 (8)**	**23 (7)**
Diarrhoea	7 (6)	11 (4)	13 (4)
Vomiting	4 (4)	9 (4)	10 (3)
Nausea	3 (3)	5 (2)	5 (2)

Source: Module 2.7.4 Table 18.1.1.13.6. Data cutoff: 29 May 2020.

PT: Preferred Term; QD: once daily; SAE: serious adverse event; SOC: System Organ Class.

Treatment-emergent adverse events (TEAEs) are defined as any adverse event that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug. A patient reporting the same event more than once has that event counted only once within each system organ class, and once within each preferred term. MedDRA Dictionary (Version 23.0) was used for coding adverse events.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of treatment-emergent SAEs; however, due to differences in grouped terms, FDA's review of treatment-emergent serious adverse events occurring in ≥2% of patients in the pooled safety population included diarrhea, dyspnea, vomiting, pyrexia, acute kidney injury, nausea, pleural effusion, and cardiac failure. The following grouped terms were included in this assessment:

- Diarrhea: diarrhea and enterocolitis
- Acute kidney injury: acute kidney injury and renal failure
- Pleural effusion: pleural effusion, malignant pleural effusion, and infectious pleural effusion
- Cardiac failure: cardiac failure, cardiac failure congestive, cardiomyopathy, and ejection fraction decreased

Diarrhea was the most common treatment-emergent SAE (8%); additional details are provided in Section 8.2.4.5.

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The FDA did not independently verify the SAEs reported to be treatment-related by the Applicant, as this distinction is difficult to definitively determine in non-randomized trials without a control arm.

8.2.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

TEAEs leading to dose discontinuation occurred in 18% of patients in the Pooled Prior Platinum Analysis Set, similar to the range in the other 2 safety populations (18% in the 160 mg QD Population to 19% in the Overall Population), with GI disorders accounting for a majority of these events (7% in each of the 3 safety populations). Diarrhoea and nausea were the most common TEAE leading to dose discontinuation across the 3 safety analysis populations (2% to 4% for each). Respiratory-related TEAEs (SOC: respiratory, thoracic, and mediastinal disorders) leading to dose discontinuation occurred in 4% of the Overall Safety Population, with dyspnoea and pneumonitis being the most common of these events (an occurrence of 2% for each of these TEAEs). This was consistent with the 160 mg Safety Population, in which 3% of patients discontinued due to a respiratory-related TEAE, with dyspnoea and pneumonitis being the most common of these events (an occurrence of ≤1% for each of these TEAEs). One subject (<1%) in the Pooled Prior Platinum Analysis Set discontinued due to interstitial lung disease among respiratory-related TEAEs. All other TEAEs leading to dose discontinuation occurred ≤2% in each of the 3 safety populations.

Within each of the 3 safety populations, TEAEs were more often managed by dose interruption, without the need for dose reduction or discontinuation. The frequency of dose discontinuation due to a TEAE was 18% to 19%, with the most common cause for discontinuation being GI disorders.

The FDA's Assessment:

FDA agrees that dose discontinuations occurred in approximately one-fifth of patients across safety populations.

GI disorders accounted for most events requiring dose discontinuation, and when using grouped terms for diarrhea, nausea, vomiting, decreased appetite and stomatitis, these events occurred in 10-14% of the 3 safety populations. Diarrhea and nausea were the most common reason for discontinuation.

Respiratory disorders that led to discontinuation, including pneumonitis, dyspnea, pneumonia, hypoxia and pleural effusion, occurred in 2-5% of patients across the 3 safety populations.

No other adverse events led to discontinuation in more than 2% of patients.

In the primary safety population (n=114), of the 19 patients (17%) who had an adverse event that led to dose discontinuation, nearly two-thirds of the events resolved. TEAEs that did not resolve included nausea, diarrhea, vision blurred, alopecia, dermatitis, pneumonitis, pericardial effusion, amylase increased, and weight decreased.

A summary of events leading to dose discontinuation in the primary safety population (n=114) is provided in Table 36 below.

Table 36: FDA Analysis of TEAEs leading to dose discontinuation in the primary safety population (n=114) (FDA table)

Adverse Event	Primary Safety Population N=114 N (%)
Diarrhea	5 (4.4)
Nausea	4 (3.5)
Vomiting	2 (1.8)
Stomatitis	2 (1.8)
Decreased appetite	2 (1.8)
Abdominal pain	1 (0.9)
Alopecia	1 (0.9)
Amylase increased	1 (0.9)
Cardiomyopathy	1 (0.9)
Clostridium Test Positive	1 (0.9)
Fatigue	1 (0.9)
Muscular Weakness	1 (0.9)
Pericardial Effusion	1 (0.9)
Pleural Effusion	1 (0.9)
Pneumonitis	1 (0.9)
Rash	1 (0.9)
Ventricular Arrhythmia	1 (0.9)
Vision Blurred	1 (0.9)
Weight Decreased	1 (0.9)

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8.2.4.4 Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

In the Pooled Prior Platinum Population, 58 patients (51%) required a dose interruption of mobocertinib because of an AE. Diarrhoea (16%), the most common TEAE leading to dose interruption, was followed by nausea and vomiting (7%).

The percentages of patients who had drug interruptions were similar in the 160 mg QD Population, with 150 patients (59%) requiring a dose interruption; interruptions due to diarrhoea occurred in 25% of patients; interruptions due to nausea and vomiting occurred in 14% of patients. Similarly, in the Overall Safety Population, 60% of patients required a study drug interruption, with diarrhoea (24%) and nausea and vomiting (14%) being the most common events leading to study drug interruption.

Overall 25% to 31% of patients across the safety analysis populations required a reduction in mobocertinib because of an AE. The most common TEAE leading to dose reduction across all 3 safety analysis populations was diarrhoea (8% to 14%); 3% to 5% of these events were Grade ≥3; with 3 events in the Overall Population deemed serious.

The FDA's Assessment:

The FDA agrees with the percentages of patients who required dose interruptions (51-60%) and reductions (25-31%) across the 3 safety populations.

Similar to dose discontinuations, GI disorders accounted for the majority of drug interruptions and reductions.

In the primary safety population (n=114), dosage interruptions due to an AE occurred in 51% of patients. TEAEs which required dosage interruption in >5% of patients included diarrhea, nausea and vomiting. Of the TEAEs that led to dose interruption, 87% of events resolved. Dose reductions due to an AE occurred in 25% of patients. The TEAE which required dose reduction in >5% of patients was diarrhea. Of the TEAEs that led to dose reduction, 77% of events resolved. See Section 8.2.4.5 for additional details regarding dose modifications for diarrhea. Table 37 provides a summary of the per-patient incidence of events leading to dose interruption or reduction.

Table 37: FDA Analysis of TEAEs leading to dose interruptions and dose reductions in ≥2% of patients in the primary safety population (n=114) (FDA table)

Adverse Event	Dose Interruptions N (%)	Dose Reductions N (%)
Diarrhea	24 (21)	11 (10)
Nausea	8 (7)	6 (5)

Vomiting	7 (6)	3 (2.6)
Stomatitis	6 (5)	3 (2.6)
Increased blood creatinine	5 (4.4)	2 (1.8)
Decreased appetite	4 (3.5)	2 (1.8)
Paronychia	4 (3.5)	3 (2.6)
Pyrexia	4 (3.5)	0
Increased amylase	3 (2.6)	0
Dyspnea	3 (2.6)	0
Increased Lipase	3 (2.6)	2 (1.8)
Musculoskeletal Pain	3 (2.6)	0
Pruritis	3 (2.6)	1 (0.9)
Rash	3 (2.6)	4 (3.5)
Fatigue	2 (1.8)	3 (2.6)

8.2.4.5 Other Adverse Events- Adverse Events of Clinical Interest

The Applicant's Position:

AEs of clinical interest (AECI) are summarized separately and were chosen based on the following factors: 1) identified by searches of the clinical database considering the context of the intended patient population; 2) adverse reactions for commercially available EGFR TKIs (eg, pneumonitis/interstitial lung disease [ILD], gastrointestinal [GI] events, skin events, cardiac events, and stomatitis); 3) AEs reported within the mobocertinib program (eg, amylase/lipase increases). The AECI selected for further presentation are pneumonitis/ILD, cardiac disorders, GI toxicities (diarrhoea, nausea, vomiting), stomatitis, skin-related events, and amylase/lipase increases. The search strategy for the selected AECI is presented in Table 38.

Table 38: TEAE of Clinical Interest: Search Strategy

TEAE of Clinical Interest	Search Strategy Used to Define the TEAE of Clinical Interest
Pneumonitis/ILD	SMQ interstitial lung disease - Narrow
Cardiac disorders	SMQ Torsades de Pointes QT prolongation – Broad
	SMQ Cardiomyopathy – Broad
	SMQ Supraventricular tachyarrhythmias – Narrow
	SMQ Myocardial infarction – Narrow

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TEAE of Clinical Interest	Search Strategy Used to Define the TEAE of Clinical Interest
GI toxicities	PTs: diarrhoea, nausea, vomiting
Stomatitis	HLT stomatitis and ulceration
Skin-related events	SOC Skin and subcutaneous tissue disorders
	HLT Skin structures and soft tissue infections
Amylase/lipase increase	SMQ Acute pancreatitis - Narrow

GI: gastrointestinal; HLGT: High Level Group Term; HLT: High Level Term; ILD: interstitial lung disease; PT: Preferred Term; SMQ: Standardised MedDRA Query; TEAE: treatment-emergent adverse event.

AECI are summarized in this Assessment Aid by relatedness, grade, seriousness, and discontinuation for each of the 3 safety populations in Table 39.

Table 39: TEAEs of Clinical Interest – Overall, Relatedness, Grade, Seriousness, Discontinuation (by Safety Population; Data Cutoff 29 May 2020)

	Pooled Prior Platinum N = 114	160 mg QD N = 256	Overall N = 325
	n (%) of Patients		
Pneumonitis/ ILD			
TEAE	2 (2)	8 (3)	12 (4)
Related	1 (<1)	4 (2)	7 (2)
Grade ≥3	1 (<1)	2 (<1)	5 (2)
Serious	1 (<1)	4 (2)	7 (2)
Discontinued	1 (<1)	5 (2)	7 (2)
Cardiac disorders			
TEAE	35 (31)	76 (30)	99 (30)
Related	16 (14)	27 (11)	31 (10)
Grade ≥3	17 (15)	32 (13)	40 (12)
Serious	14 (12)	26 (10)	34 (10)
Discontinued	2 (2)	5 (2)	9 (3)
GI toxicities			
TEAE	108 (95)	245 (96)	301 (93)
Related	106 (93)	240 (94)	290 (89)
Grade ≥3	28 (25)	56 (22)	63 (19)
Serious	13 (11)	21 (8)	26 (8)
Discontinued	9 (8)	16 (6)	20 (6)
Stomatitis			
TEAE	42 (37)	85 (33)	97 (30)
Related	40 (35)	80 (31)	89 (27)
Grade ≥3	5 (4)	9 (4)	10 (3)
Serious	0	0	0

Table 39: TEAEs of Clinical Interest – Overall, Relatedness, Grade, Seriousness, Discontinuation (by Safety Population; Data Cutoff 29 May 2020)

	Pooled Prior Platinum N = 114	160 mg QD N = 256	Overall N = 325
	n (%) of Patients		
Discontinued	2 (2)	2 (<1)	2 (<1)
Skin-related events			
TEAE	103 (90)	217 (85)	261 (80)
Related	102 (89)	211 (82)	247 (76)
Grade ≥3	5 (4)	12 (5)	12 (4)
Serious	0	0	1 (<1)
Discontinued	1 (<1)	3 (1)	3 (<1)
Amylase/Lipase Increased			
TEAE	87 (76)	185 (72)	228 (70)
Related	72 (63)	152 (59)	180 (55)
Grade ≥3	15 (13)	29 (11)	36 (11)
Serious	11 (10)	18 (7)	22 (7)
Discontinued	7 (6)	11 (4)	12 (4)

Source: Module 2.7.4 18.1.1.16.1B, 18.1.1.16.1C., 18.1.1.16D. Data cutoff: 29 May 2020.

GI: gastrointestinal; ILD: interstitial lung disease; QD: once daily; TEAE: treatment-emergent adverse event.

Note: TEAEs are defined as any AE that occurs time from first dose of study drug and through the end of treatment until 30 days after the last dose of study drug. A patient reporting the same event more than once has that event counted only once within each system organ class and once within each preferred term. Patients with one or more adverse events within a level of MedDRA term are counted only once in that level. MedDRA Dictionary (Version 23.0) was used for coding adverse events.

The time-to-onset of each TEAE of clinical interest was summarized from the first dose date to the TEAE onset date. If a patient had multiple events in the same category of clinical interest, only the earliest event was counted. Summaries of time-to-onset were provided for only the subset of patients who experienced that event in each analysis population.

Grade 5 events are outlined in Section 8.2.4.1.

Pneumonitis/ILD

The rates of the AECI of pneumonitis/ILD were similar across the 3 safety populations (2% to 4%) (Table 39). The most common event within this AECI category was pneumonitis (<1% to 3% of patients). Pneumonitis/ILD AECI events that were Grade ≥3, serious, or led to discontinuation of study dosing, were experienced in <1% to 2% of patients across the 3 safety populations (Table 39). Pneumonitis/ILD was observed across dose levels 80 mg to 160 mg; 1 patient died due to pneumonitis (dosed at 120 mg QD of mobocertinib).

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Cardiac disorders

The search strategy for the cardiac disorders AECI is conservatively broad and the SMQs used in this search include both cardiac and respiratory SOC terminology. With this search strategy 30% to 31% of patients across all 3 populations reported a TEAE within the cardiac disorders AECI (Table 39). The only event reported in more than 10% of patients was dyspnoea (13% to 18%), which is a nonspecific event and does not necessarily reflect a cardiac problem. It is notable that at the time of Study 101 enrollment approximately 54% of patients who received 160 mg QD while on study (Study 101 expanded analysis set) reported a respiratory comorbidity at baseline and 32% to 42% of patients depending on the specific population had cancer involving both lungs.

As noted previously, the most frequently occurring TEAE by PT for this AECI, was dyspnoea (13% to 18%); electrocardiogram QT prolonged (6% to 10%) was the next most common PT. There were no TEAEs of QT prolonged that were deemed serious or led to study drug discontinuation, 2% to 4% of patients experienced a QT prolongation event that was Grade ≥3. One SAE of ventricular arrhythmia was reported to be associated with Torsades de Pointes, was assessed as related, led to discontinuation of mobocertinib, and is described below. Across the 3 safety populations, cardiac failure (n = 2), cardiac failure congestive (n = 1), cardiomyopathy (n = 1), and ejection fraction decreased (n = 2) were reported. The majority of these events were serious and related although most did not lead to discontinuation of mobocertinib. One event of cardiac failure was fatal and assessed as related to mobocertinib.

A separate unblinded DMC for Study 101 evaluated the results of safety analyses and made recommendations to the Applicant as needed. One recommendation from the DMC, a review by an independent cardiac consultant was completed. An enhanced cardiac monitoring (such as left ventricular ejection fraction assessment by ECHO or MUGAs) which is consistent with similar drugs in this class, was recommended. The assessments were added to new and ongoing studies and not Study 101, given that Study 101 had already completed enrollment and patients had been on study for a median >8 months at the time of the recommendation.

Summary Narratives of Events of Interest

Summary narratives of patients who died on study are provided in the CSR for Study 101. One of these events, cardiac failure, was fatal and deemed potentially related to study dosing. This event is summarized as follows:

- A 68-year-old male patient (former smoker) experienced serious cardiac failure (Grade 4) on Study Day 90 (study dosing was discontinued the day before this event). Cardiac failure was considered related to the study drug by the investigator and was ultimately fatal. The patient had a concurrent medical history of coronary artery disease without angina pectoris and a previous echocardiogram demonstrating an ejection fraction of 55% to 60%. On Study Day 90 the patient had nonserious Grade 3 tachycardia, deemed not related to study dosing; nonserious Grade 2 nausea and vomiting deemed related to study dosing; nonserious Grade 3 pneumonia and Grade 1 wheezing, both deemed not related to study dosing; nonserious creatinine increase, initially a Grade 1 on Study Day 16, progressing to Grade 2 on Study

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Day 90, and Grade 3 on Study Day 96. Grade 1 dehydration was noted on Study Day 29, advancing to Grade 2 on Study Day 90.

At the time the patient presented with cardiac failure, an echocardiogram revealed a cardiomyopathy with an ejection fraction of 20%, borderline left ventricular dilation, and pulmonary hypertension. Troponin levels were 118. An electrocardiogram was fairly unremarkable and showed sinus tachycardia with a leftward axis and occasional premature ventricular contractions. The patient progressed to renal failure approximately 2 days after presenting with cardiac failure and dialysis treatment was initiated. The patient was treated with symptomatic measures for heart failure including but not limited to B1-agonist agent, anti-diuretics, IVF, and analgesics. The patient died on Study Day 97 due to worsening cardiac failure.

Summary narratives of patients who had treatment-emergent SAEs are provided in the CSR for Study 101. One of these events, ventricular arrhythmia, is summarized as follows:

- A 74-year-old female patient (nonsmoker) experienced serious ventricular arrhythmia on Study Day 204, which was assessed as related to study drug and led to study drug discontinuation. Prior to the event, the patient had multiple nonserious events of ECG QT prolonged, including 1 Grade 3 event that led to a 2-week study drug interruption from Day 86 to 98. Onset for nonserious events of QT prolonged ranged from Day 37 through Day 208 (Study 101 Listing 16.2.7.b). The patient also had multiple Grade 1 GI events leading up to the SAE of ventricular arrhythmia, including diarrhoea, nausea, vomiting, and abdominal pain upper, and decreased appetite. Study drug was restarted at 160 mg on Day 99 and continued until on Day 204 when the patient collapsed while talking and lost consciousness suddenly due to cardiac arrest (suspected to be related to Torsades de Pointes), received cardiopulmonary resuscitation, regained consciousness, and was sent to the emergency room. The patient was diagnosed with Grade 4 life-threatening ventricular arrhythmia and was hospitalized. Study drug was permanently discontinued due to the event. The patient had frequent premature ventricular complexes and bigeminy. An ECG showed sinus rhythm with frequent bigeminy premature ventricular complexes and QT interval prolonged (QTcF: 548 ms). On the same day, the patient had hypomagnesaemia (Grade 2 [1.73 mmol/L]) and hypokalaemia (Grade 2 [3.0 mmol/L]). The physician prescribed magnesium sulfate, Primperan (metoclopramide hydrochloride), potassium gluconate, potassium chloride, tramadol, and magnesium chloride. An ECG a few hours later showed torsade de pointes, and the patient lost consciousness for a few seconds (troponin 83.91 ng/L). The patient was transferred to the cardiology intensive care unit for close observation. After admission, sustained ventricular tachycardia without pulsation was noted. The patient experienced seizures and was in and out of consciousness. Cardiopulmonary resuscitation was administered, and within 1 minute, she was cardioverted to sinus rhythm (200 joule direct-current shock). Follow-up labs included: potassium 4.6 mmol/L and magnesium 1.29 mmol/L.

  On the following day, the patient again was cardioverted for another bout of ventricular tachycardia. She received a temporary venous pacemaker for frequent ventricular tachycardia and had clear consciousness. A chest x-ray showed cardiomegaly, tortuous aorta with wall

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calcification, ill-defined opacity, and nodular shadows at bilateral lung fields, bilateral sharp costophrenic angles, pleural thickening at right apical lung, and (previous) fracture at left ribs. Treatment medications included Trandate (labetalol), Xylocaine (lidocaine), carvedilol, metoprolol succinate, Bfluid (amino acid and glucose injection with electrolytes and vitamin B1), Vitacal (calcitriol, calcium carbonate, folic acid, methylcobalamin and pyridoxine), multivitamins and dextrose, ambroxol hydrochloride, and electrolyte solution. Xylocaine was tapered off and the patient returned to sinus rhythm.

Two days later, the patient's labs included: potassium 4.1 mmol/L and, magnesium 0.72 mmol/L. The temporary pacemaker was removed. Three days later, the patient's ECG showed sinus rhythm with occasional ventricular premature contractions and a QTc 480 msec. The patient was discharged from the hospital the same day, approximately 6 days after admission, under generally stable condition.

GI Toxicities

The majority of patients reported an AECI of GI toxicity (ie, diarrhoea, nausea, and vomiting) within each of the 3 safety populations (Table 39), with diarrhoea being the most common of these events. AECI GI toxicities leading to discontinuation of study dosing was experienced by 6% to 8% of patients.

Diarrhoea

A majority of TEAEs in the AECI of GI toxicity were diarrhoea. Diarrhoea was frequently reported as related to study drug and Grade ≤2, with a median time-to-onset of 5 days, in each of the 3 safety populations. The rate of patients experiencing a serious event of diarrhoea was consistent at 5% to 8% in each of the safety analysis populations with 4% of patients in each of the 3 safety populations requiring discontinuation of study drug due to events of diarrhoea. Anti-diarrhoeal medications were frequently dosed for symptom management; the most common agent used was loperamide (coded either as loperamide [23% to 26%]; loperamide hydrochloride [44% to 46%]; or loperamide; simeticone [≤1%]), followed by Lomotil (code as Lomotil [6% to 14%]; atropine sulfate, diphenoxylate hydrochloride [2% to 5%]; and atropine; diphenoxylate [<1% to 2%]).

Nausea/Vomiting

Nausea and vomiting symptoms were the second most common AECI GI toxicities reported in the 3 safety analysis populations (nausea: 40% to 45%; vomiting: 34% to 37%), patients experiencing an event deemed related to study drug dosing ranged from 25% to 30% for vomiting; and, 32% to 39% for nausea. The majority of events of diarrhoea, vomiting, or nausea were Grade 1 or 2 and the number of patients experiencing an event that resulted in dose discontinuations was 2% to 4%. The rate of patients experiencing a serious event of vomiting was 4% and of nausea 2% to 3% in each of the safety analysis populations. The most common concomitant medications for symptomatic management of nausea and/or vomiting included omeprazole (20% in each safety population), ondansetron (13% in each safety population), and metoclopramide (9% to 12%). The time-to-onset for nausea or vomiting was within the first few

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weeks of dosing was assessed participants in Part 3. The median time-to-onset for nausea and vomiting was 27.5 days for each TEAE among patients in Part 3.

Possible clinical sequelae of AECI GI toxicities such has diarrhoea, nausea, and vomiting may include dehydration, electrolyte imbalance, and impact on the renal system. Dehydration was infrequent (9% to 12%) and electrolyte imbalance (mineral and electrolyte analyses) was noted in 2% to 4% of patients across the 3 safety populations. Elevations in creatinine ranged from 25% to 32% of patients in each of the safety populations with the highest rates noted in patients who identified as Asian. The reason for this difference may represent a reporting difference by investigators but that is not completely clear (Pooled Prior Platinum: 35%; Overall: 25%; 160 mg QD: 29%).

In summary, gastrointestinal toxicity events, including diarrhoea, vomiting, and nausea, are among the most frequently reported TEAEs for mobocertinib, similar to other EGFR TKIs, as these are mechanism-related. AECI GI toxicity events were predominately low grade, with few events deemed serious or resulting in discontinuation of mobocertinib. As such, for the majority of patients these events were generally tolerable, monitorable, and manageable with standard supportive care (eg, anti-diarrhoeal medication for diarrhoea and antiemetic medications for nausea and/or vomiting).

Stomatitis

Oral stomatitis is a common known risk for other EGFR TKIs and was a common TEAE with mobocertinib dosing across the safety populations, with the majority of the stomatitis events being Grade 1 or 2 (approximately 96%), and reported as related to study drug (27% to 35%). None of these events were deemed serious. A limited number of stomatitis events (≤2% across the 2 safety populations) led to dosing discontinuation (Table 39). A variety of oral preparations and mouthwashes were used according to standard medical practice.

Skin-Related Events

Skin-related events, including rash and paronychia are a common known risk of other EGFR TKIs. There is some variety in the characterization of TEAEs of the skin resulting in different preferred terms to describe it, therefore a review was done using broad high level search terminology for AECIs (Table 38).

A majority of patients in each of the safety populations had TEAEs that were skin-related (Table 39). Of the skin-related AECIs, most were deemed related to study dosing and were Grade 1 to 2 (Grade ≥3: 4% to 5%) (Table 39). Few events (≤1%) led to discontinuation of study dosing and 1 event was deemed serious (Table 39). No severe cutaneous events (ie, Stevens-Johnson syndrome or epidermal necrolysis), were observed across the mobocertinib clinical program.

In summary, skin-related events, including events such as rash, dry skin, and paronychia, are among the most frequently reported TEAEs for mobocertinib as well as for other EGFR TKIs as these are mechanism-related events.

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Amylase/lipase Increase

The SMQ for acute pancreatitis was used to examine elevations of amylase/lipase seen in this study, as pancreatitis has been reported with other EGFR TKIs. Although 70% to 76% of patients had an event using this AECI search methodology, the majority of the events reported were nausea and vomiting (37% to 45% and 34% to 40%, respectively across populations) and not necessarily related to amylase/lipase increase (see previous nausea/ vomiting section for further details). In the 3 safety populations, an increase in amylase was reported in 20% to 22% of patients; an increase in lipase was reported in 14% to 18% of patients.

Still using the broad SMQ, events associated with this AECI were common in each of the safety analysis populations, with most being deemed related to study dosing; however, few were Grade ≥3, deemed serious, or led to study drug discontinuation (Table 39).

The FDA's Assessment:

The TEAEs of clinical interest selected by the Applicant, including cardiac disorders, pneumonitis/ILD, GI toxicities, stomatitis, skin-related events, and elevation of amylase/lipase, were evaluated independently by the FDA, in addition to other TEAEs of clinical interest identified during the review.

QTc Prolongation and Torsades de Pointes

QTc prolongation was identified as an important risk during the review period. Product labeling for mobocertinib includes a boxed warning for QTc prolongation and Torsades de Pointes due to this potentially life-threatening or fatal risk, which may be mitigated with appropriate management including monitoring of electrolytes, routine ECG assessments, and avoiding concomitant use of drugs known to prolong the QTc interval.

The original protocol for Study 101 excluded patients with prolonged QT interval on screening electrocardiogram (ECG), defined as QTcF of >450 msec in males or >470 msec in females, as well as patients being treated with medications known to be associated with the development of Torsades de Pointes.

ECG assessments required during the trial included triplicate ECGs at baseline on Cycle 1, Day 1 before the first administration of mobocertinib; and triplicate ECGs on Cycle 2, Day 1 (Day 29) prior to administration of the Cycle 2, Day 1 dose; and at 1, 2, 4, and 6 hours after dosing of TAK-788 on Cycle 2, Day 1. Subsequently, single ECGs were performed every 4 weeks for the main treatment period (first 3 years of treatment).

In the pooled safety population (n=256), TEAEs of QTc prolongation occurred in 7% (n=17) of patients, including 2% of patients with Grade 3 events; there were no fatalities (Table 40). In 12 patients with Grade 1 or 2 events, the same dose of mobocertinib was continued and 83% resolved. In 5 patients with Grade 3 events, mobocertinib was interrupted in 4 of 5 cases and all of these events resolved. In one patient with Grade 3 QTc prolongation, the mobocertinib dose was not changed and the event did not resolve.

In addition, one serious TEAE of Grade 4 ventricular arrhythmia and Torsades de Pointes occurred in the setting of recurrent events of QTc prolongation and electrolyte abnormalities in a 74-year-old female (Subject TAK78801-788101-[redacted] (b) (6)) as described by the Applicant in the narrative above, in whom mobocertinib was permanently discontinued.

Table 40: FDA Analysis of Patients with TEAEs of QTc prolongation or ventricular arrhythmia in 3 safety populations (FDA table)

TEAEs of QTc Prolongation	Overall safety population N=325 N (%)	Pooled safety population N=256 N (%)	Primary safety population N=114 N (%)
All Grades	20 (6)	17 (7)	11 (10)
Grade 3	6 (2)	5 (2)	3 (3)
Grade 4	1 (<1)	1 (<1)	1 (1)
Grade 5	0	0	0

In the 90-day safety update (Data Cut-off date November 1, 2020), there were 3 additional TEAEs of QT prolongation (none were serious, ≥ Grade 3, or led to treatment discontinuations), which increases the number of all grade events in the primary safety population to 14 patients (12%).

The clinical events of QTc prolongation including a life-threatening Grade 4 event of Torsades de Pointes and the resolution of Grade 3 events of QTc prolongation with mobocertinib interruption, in the context of concentration-QTc analyses that show mobocertinib treatment is associated with significant QTc prolonging effect, suggest that QTc prolongation may be attributable to mobocertinib. The product labeling includes a boxed warning for QTc prolongation and Torsades de Pointes, as well as monitoring and dose modification recommendations based on the severity of QTc prolongation. The Applicant will conduct an integrated analysis of QTc prolongation and related events from randomized clinical trials to further characterize this identified safety signal.

Additionally, ECGs from a subset of 250 patients who had at least one baseline ECG and one subsequent scheduled or unscheduled ECG were analyzed to further characterize the risk of QTc prolongation. Of these 250 patients, 1.2% had a QTc interval >500 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. See Section 6.3.1 for further detail.

Interstitial Lung Disease/Pneumonitis:

TEAEs of pneumonitis were identified by the Applicant using the preferred terms pneumonitis and interstitial lung disease (ILD). The FDA analysis of ILD/pneumonitis also included a review of additional preferred terms from the Respiratory Disorders system organ class (SOC), including

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respiratory failure and dyspnea. Clinical narratives for all potential events of pneumonitis were reviewed independently by the FDA to assess the likelihood of attribution to mobocertinib.

In the pooled safety population (n=256), 8 patients had TEAEs with the preferred terms pneumonitis or ILD. In addition, there were 5 patients with events of respiratory failure, 44 patients with events of dyspnea, and 12 patients with events of hypoxia.

Three of the 5 patients with respiratory failure had fatal events that were consistent with possible pneumonitis based on review of the narratives (Subjects AP32788-15-101-(b) (6), AP32788-15-101-(b) (6), and TAK78801-788101-(b) (6)). One patient had Grade 4 respiratory failure consistent with disease progression (Subject AP32788-15-101-(b) (6) and one patient had Grade 3 respiratory failure that occurred simultaneously with a Grade 2 event of pneumonitis (Subject AP32788-15-101-(b) (6)).

The clinical narratives for the 44 patients in the pooled safety population with Grade 3 or higher events of dyspnea were consistent with underlying disease or infectious pneumonia, except for one event of Grade 3 dyspnea which occurred simultaneously with the event of Grade 5 respiratory failure due to pneumonitis described above (Subject AP32788-15-101-(b) (6)).

The clinical narratives for the 12 patients in the pooled safety population with Grade 3 or higher events of hypoxia were consistent with underlying disease or infectious pneumonia, except for one event of Grade 3 hypoxia which occurred simultaneously with the event of Grade 5 respiratory failure due to pneumonitis described above (Subject AP32788-15-101-(b) (6)).

Based on FDA's review, 10 patients (4%) in the pooled safety population had TEAEs of ILD/pneumonitis (Table 41). Mobocertinib was either interrupted or discontinued in all cases and only 2 patients recovered. Half of these events were Grade 3 or higher and three events (30%) resulted in death. An additional patient in the overall safety population (n=325) who received mobocertinib 120 mg once daily had a Grade 5 adverse event of pneumonitis.

Table 41: FDA Analysis of Patients with ILD/Pneumonitis in the Pooled Safety Population (n=256) (FDA table)

Subject ID	Demographics	TEAE preferred term(s)	Highest Grade Event	Action taken
AP32788-15-101-(b) (6)	64-year-old White female	Pneumonitis/ Respiratory Failure	5	Drug interrupted
AP32788-15-101-(b) (6)	65-year-old White male	Respiratory failure	5	Drug interrupted

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Subject ID	Demographics	TEAE preferred term(s)	Highest Grade Event	Action taken
TAK78801-788101-(b) (6)	53-year-old White male	Respiratory failure	5	Drug interrupted
TAK78801-788101-(b) (6)	72-year-old Asian female	Interstitial lung disease	3	Drug withdrawn
TAK-788-1003-(b) (6)	55-year-old Asian male	Interstitial lung disease	3	Drug withdrawn
AP32788-15-101 (b) (6)	28-year-old White female	Pneumonitis/Acute Respiratory Failure	3	Drug interrupted
AP32788-15-101-(b) (6)	55-year-old Asian female	Pneumonitis	2	Drug withdrawn
TAK-788-1003-(b) (6)	65-year-old Asian male	Pneumonitis	2	Drug withdrawn
TAK78801-788101-(b) (6)	69-year-old White female	Pneumonitis	2	Drug interrupted
AP32788-15-101-(b) (6)	38-year-old White male	Pneumonitis	1	Drug withdrawn

In accordance with the potential severity of drug-induced ILD/pneumonitis, previous experience with other agents in this class, and clinical data from Study 101, the Warnings and Precautions section of product labeling for mobocertinib describes the serious risk of ILD/pneumonitis and recommends permanent discontinuation of mobocertinib for confirmed cases of ILD/pneumonitis.

Cardiac Toxicity:

Cardiac Failure:

The FDA's assessment of the risk of cardiac failure included the preferred terms cardiac failure, cardiac failure congestive, cardiomyopathy and ejection fraction (EF) decreased. Given the severity and rarity of these events, FDA reviewed data from the overall safety population (n=325), in which there were 7 patients with an adverse event of cardiac failure, including 2 patients with non-serious Grade 2 events (n=1 cardiac failure, n=1 EF decreased). Five events were Grade 3 or greater in severity, and are described below:

- Subject TAK78801-788101 (b) (6): 58-year-old male described in the Applicant's narrative above with **Grade 5 cardiac failure**, assessed as related to mobocertinib.

- Subject AP32788-15-101-(b) (6): 59-year-old female who developed shortness of breath approximately 1 year and 9 months after starting treatment. She was hospitalized and

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diagnosed with **Grade 4 cardiomyopathy** (EF 28.5%) in the setting of a large non-malignant pleural effusion requiring thoracentesis. The event was attributed as related, the drug was discontinued, and the patient recovered.

- Subject AP32788-15-101-(b) (6): 58-year-old male who developed shortness of breath and lower extremity edema approximately 7 months after starting mobocertinib. He was hospitalized and diagnosed with **Grade 3 cardiac failure congestive** (EF 20-25%) without evidence of ischemia, myocarditis or infiltrative disease. The event was attributed as related, the drug was discontinued, and the event was not resolved at the time of last follow-up.

- Subject TAK78801-788101-(b) (6): 72-year-old female who developed nausea, vomiting and poor oral intake approximately 4 weeks after starting treatment. She was hospitalized and diagnosed with **Grade 3 ejection fraction decreased** (EF 25%) in the setting of hypovolemia and acute kidney injury. The event was attributed as related, the drug was discontinued due to the nausea, and the patient recovered.

- Subject AP32788-15-101-(b) (6): 70-year-old female who was hospitalized approximately 3 weeks after starting treatment due to hyponatremia in the setting of nausea and decreased appetite. While admitted she developed acute right-sided weakness and aphasia, and neuroimaging showed a left temporal acute ischemic stroke (grade 3 cerebrovascular accident) in the setting of bilateral deep venous thromboses. She also had elevated serum troponin and ST elevation on ECG and was diagnosed with **Grade 3 stress cardiomyopathy** (EF 25% with left ventricular global hypokinesis), which a Cardiology consultant diagnosed as consistent with stress cardiomyopathy but could not rule out an ischemic etiology. Despite escalating care, she developed worsening kidney function and died one week after admission. The event of stress cardiomyopathy remained unresolved at the time of death and was attributed as not related to mobocertinib.

In addition to the cardiac events with the preferred terms listed above, there was one patient in the overall safety population who had a fatal event of respiratory failure that the FDA assessed as consistent with cardiac failure with the details as follows:

- Subject AP32788-15-101-(b) (6): 63-year-old woman who developed dyspnea two weeks after starting treatment and was hospitalized for tachycardia, hypoxia and lethargy. CXR showed unchanged pleural effusion and atelectasis; diagnosed with Klebsiella UTI; treated with antibiotics and steroids including empiric treatment for pneumocystis pneumonia. An ECHO the day of admission showed stress induced cardiomyopathy and decreased EF (no value reported) with worsening hypoxia. CT did not show any parenchymal process to explain acute hypoxia. Repeat echocardiograms showed worsening ventricular dysfunction with elevated BNP and troponin. The patient developed worsening hypotension requiring blood pressure support and she died due to **Grade 5 respiratory failure** 5 days after admission.

In the mobocertinib once daily population (n=256), cardiac failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of cardiac failure.

While the original protocol did not include screening assessments with ECHO or MUGA scans, all ongoing studies with mobocertinib include left ventricular ejection fraction monitoring given the identified risk of cardiac failure; this recommendation is also included in product labeling. The Warnings and Precautions section of product labeling for mobocertinib describes the serious risk of cardiac failure and recommends permanent discontinuation of mobocertinib for ≥ Grade 2 heart failure or Grade 3 or 4 decreased EF. The Applicant will conduct an integrated analysis of cardiac failure and related events from randomized clinical trials to further characterize this identified safety signal as a post-marketing requirement.

Cardiac Conduction Abnormalities Other Than QTc Prolongation:

In addition to adverse reactions of QTc prolongation and Torsades de Pointes, other ECG abnormalities occurred in patients receiving mobocertinib. In the mobocertinib once daily population (n=256), these included 4 patients with atrial fibrillation (1.6%) and 1 patient each with ventricular tachycardia (0.4%), first degree atrioventricular block (0.4%), second degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%) and ventricular extrasystoles (0.4%).

Three events of atrial fibrillation were Grades 1 or 2, non-serious, and resolved without dose modification. The fourth event of atrial fibrillation occurred in a 55-year-old male (Subject AP32788-15-101-(b) (6)) who was taking mobocertinib for approximately one month when he developed shortness of breath and palpitations and was hospitalized for **Grade 3 atrial fibrillation** with rapid ventricular rate requiring treatment with diltiazem, amiodarone and nifedipine. The study drug was interrupted, and the event was assessed by the investigator as possibly related to mobocertinib. After 5 days he recovered and was discharged from the hospital.

One serious event of **Grade 3 ventricular tachycardia** occurred in a 64-year-old woman (Subject TAK78801-788101-(b) (6)) who was seen in the emergency department for a seizure approximately 3.5 months after starting treatment and a screening ECG showed non-sustained ventricular tachycardia. She was treated with amiodarone, and mobocertinib was held for 2 days at which time the event grade was decreased to Grade 2. The event was attributed as possibly related to mobocertinib, although concomitant medications, tiotropium bromide or fluticasone which possess arrhythmic effects, could have contributed to the event.

One serious event of asymptomatic **Grade 2 left bundle branch block** occurred in a 63-year-old male (Subject AP32788-15-101(b) (6)) with a history of hypertension who had been taking mobocertinib for approximately 2 years. Laboratory and diagnostic evaluations were unrevealing,

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including serum troponin and echocardiogram (LVEF 66%). The mobocertinib dose was not modified and the event did not resolve.

The events of first- and second-degree AV block, as well as the events of supraventricular and ventricular extrasystoles were Grade 1 and the mobocertinib dose was not modified. All of these events were assessed by the investigator as possibly related to mobocertinib. The event of first-degree AV block did not resolve, while the other events resolved within 1 to 30 days.

In the overall context of the adverse cardiac events and size of the safety database, although most cardiac conduction abnormalities other than QTc prolongation were mild, it is possible that mobocertinib contributed to these events. The Warnings and Precautions section of product labeling for mobocertinib describes these events of cardiac conduction abnormalities.

GI Disorders

Diarrhea was the most common TEAE overall, the most common high-grade TEAE, and the most common reason for drug interruption, reduction and discontinuation. In the primary safety population (n=114), the median time to onset of an individual patient's first episode of diarrhea was 5 days. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days with a range from 0 to 605 days.

Study 101 was revised in October 2018 (Amendment 4) to require loperamide prophylaxis at the first sign of diarrhea; although there were a similar number of TEAEs of diarrhea before and after (92-93%) the amendment, there was a decreased number of dose reductions due to diarrhea after the amendment (8%) compared to prior (18%).

Diarrhea resolved in the majority (n=9) of the 11 patients (10%) in the primary safety population (n=114) who had a dose reduction due to diarrhea. Of the 5 patients (4.4%) who discontinued mobocertinib for diarrhea, 80% had resolution of their diarrhea following discontinuation.

Of the 24 patients (21%) with Grade 3 diarrhea and 1 patient with Grade 4 diarrhea, 44% had a dose interruption, 20% had a dose reduction and 8% discontinued mobocertinib. All but one event of high-grade diarrhea resolved.

Other common GI disorders that occurred in ≥15% of patients in the pooled prior platinum population included stomatitis, vomiting, nausea, decreased appetite, weight decreased, abdominal pain and weight decreased (Table 42).

Table 42: FDA Analysis of GI Toxicities in the Pooled Prior Platinum Population (n=114) (FDA table)

Primary safety population (n=114)	All grade TEAEs (%)	≥ Grade 3 TEAEs (%)	SAEs (%)	Dose Modifications (%) Interruptions/Reductions/ Discontinuations			All grade TEAEs resolved (%)
Diarrhea	92	22	8	21	10	4.4	89
Stomatitis	46	4.4	0	5	2.6	1.8	78
Vomiting	40	2.6	4.4	6	2.6	1.8	86
Nausea	37	4.4	2.6	7	5	3.5	63
Decreased appetite	39	0.9	0.9	3.5	1.8	1.8	57
Weight decreased	21	0	0	0	0.9	0.9	37
Abdominal pain	18	1.8	1.8	0.9	0	0.9	68
Gastroesophageal reflux disease	15	0	0	0	0	0	47

Acute Kidney Injury

Treatment-emergent adverse events of acute kidney injury (AKI), including the preferred terms of acute kidney injury, glomerular filtration rate decreased, renal impairment, creatinine renal clearance decreased and renal failure, occurred in 7% of patients in the pooled safety population (n=256), with Grade 3 or 4 events and SAEs in 3% and 3.5% of patients, respectively. Dose modifications for AKI included dose interruption in 2% of patients, dose reduction in 1 patient and no discontinuations. Seventy-nine percent (79%) of all TEAEs of AKI resolved and all Grade 3 or higher AKI TEAEs resolved.

In addition, 52% of patients had worsening serum creatinine from baseline; 2.7% of these events were of Grade 3 or greater severity.

The FDA performed an assessment of whether AKI observed in Study 101 was due to diarrhea with dehydration and pre-renal AKI; however, only 20% of AKI events occurred within 7 days of the onset of diarrhea events.

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There was one **event of Grade 5 renal insufficiency** that occurred 32 days after mobocertinib was discontinued due to disease progression in a 72-year-old male (Subject TAK78801-788101-(b) (6)) with a history of hypertension and diabetes mellitus. He had a normal creatinine at baseline and on Day 12 of treatment, he developed Grade 1 increased serum creatinine which worsened to Grade 2 on Day 113 of treatment and did not resolve; he also had intermittent Grade 1 TEAEs of increased BUN. He was on treatment for approximately 6.5 months, then discontinued mobocertinib due to disease progression. Two days after discontinuation of treatment, he developed incomplete intestinal obstruction with nausea, vomiting and no bowel movements. Four days later he developed Grade 4 renal insufficiency and he started dialysis. Evaluation of his ascites fluid showed evidence of adenocarcinoma cells, and he transitioned to hospice and died 13 days after admission. The investigator attributed the cause of death to Grade 5 renal insufficiency and discontinuation of treatment; however, it is possible that treatment with mobocertinib contributed to his renal insufficiency.

AKI is included in product labeling as a clinically relevant adverse reaction occurring in <10% of patients in the primary safety population.

Amylase/Lipase Increase

While there were no TEAEs of pancreatitis, 25% of patients in the pooled safety population (n=256) had TEAEs of elevated amylase or lipase, including 7% of patients with Grade 3 or 4 events; there were no SAEs or fatal events of elevated amylase or lipase.

In the evaluation of laboratory abnormalities worsened from baseline, increased amylase occurred in 40% of patients (13% were Grade 3 or 4) and increased lipase occurred in 35% (10% were Grade 3 or 4).

Fifty-one patients (20%) had TEAEs of elevated amylase; of these events, 88% were Grade 1 or 2, 11% were Grade 3 and 1% were Grade 4. Dose modifications for elevated amylase included dose interruption in 2.7% of patients; 1 patient had a dose reduction and 1 patient discontinued mobocertinib. Sixty-six percent (66%) of any grade TEAEs of elevated amylase resolved and 80% of grade 3 or higher TEAEs resolved.

Thirty-nine patients (15%) had TEAEs of elevated lipase; of these events, 78% were Grade 1 or 2, 18% were Grade 3 and 4% were Grade 4. Dose modifications for elevated lipase included dose interruption in 3.1% of patients and dose reduction in 1.2%; no one required discontinuation of mobocertinib due to elevated lipase. Eighty-two percent (82%) of any grade TEAEs of elevated lipase resolved and 94% of Grade 3 or higher TEAEs of elevated lipase resolved.

Of the 17 patients with Grade 3 or 4 events of elevated amylase or lipase, 3 patients (18%) had elevated lipase alone, 3 patients (18%) had elevated amylase alone, and 11 patients (65%) had both elevated simultaneously (although both were not necessarily Grade 3 or 4). In review of any other TEAEs during the 2-week period around the event of high-grade elevated amylase or lipase, 3 of 17 had preceding events of abdominal pain; none were SAEs.

The following 3 patients had Grade 4 events of increased amylase or lipase:

- Subject TAK78801-788101-(b) (6): 53-year-old female with baseline Grade 3 amylase elevation of salivary source that remained elevated throughout treatment; on Study Day 220 she developed asymptomatic **Grade 4 increased amylase** and on the same day she came off treatment due to disease progression; she had other ongoing AEs of dry mouth, dysgeusia and diarrhea; there were no other symptoms related to increased amylase; the lipase levels throughout were low or normal; the outcome of the event was "unknown".
- Subject AP32788-15-101-(b) (6): 66-year-old female with normal baseline amylase and lipase who developed intermittent events of elevated amylase and lipase throughout treatment. Starting on Study Day 57, she developed **Grade 4 increased lipase** with Grade 3 increased amylase; mobocertinib was held until approximately one week later when the events improved to Grade 2 severity and mobocertinib was restarted at a reduced dose of 120 mg. On Study Day 113, she experienced a second episode of asymptomatic **Grade 4 increased lipase** with Grade 1 increased amylase. There was no evidence of pancreatitis on CT imaging. Mobocertinib was held for one week, then restarted at the same dose when the increased lipase improved to Grade 3 severity. She had ongoing intermittent events of increased amylase and lipase between Study Days 120 to 295, ranging from Grades 1 to 3, which were unresolved as of the last data cut-off date. As of the data cut-off date, treatment was ongoing with a partial tumor response.
- Subject AP32788-15-101-(b) (6): 63-year-old male with baseline Grade 1 amylase and lipase elevations who developed **Grade 4 increased lipase** and Grade 3 increased amylase on Study Day 15. Mobocertinib was held for 1 week until the events resolved, and mobocertinib was restarted at a reduced dose of 120 mg. On Study Day 29, he had recurrent Grade 3 increased lipase and Grade 1 increased amylase, and the dose was held until the lipase elevation improved to Grade 1; he then resumed mobocertinib at the same dose. On Study Day 71, he had recurrent Grade 3 increased lipase; the dose was held until resolution one week later, and he restarted mobocertinib at a reduced dose of 80 mg with no further events. He stopped treatment on Study Day 134 due to progressive disease.

Because of the lack of clinical symptoms of pancreatitis with elevations of serum amylase and lipase, resolution of most events without dose modification, and without an associated diagnosis of pancreatitis, these lab abnormality events were not considered serious or to have implications for prescribing decisions. Therefore, they were not included in Section 5 of product labeling for mobocertinib.

Skin-Related Events

Rash was the second most common TEAE after diarrhea. Using the grouped term for rash (including preferred terms rash, dermatitis acneiform, rash maculo-papular, rash pustular, dermatitis, urticaria, acne, rash pruritic, rash papular, vulvovaginal rash, rash vesicular, rash erythematous and rash macular), TEAEs of any grade occurred in 73% of patients in the pooled

safety population (n=256). Most events were mild to moderate in severity; 3.1% of patients had Grade 3 or 4 TEAEs and there were not rash-related SAEs. Dose modifications for rash included dose interruption in 9%, dose reduction in 5% and 3 patients discontinued mobocertinib due to rash. In the primary safety population (n=114), a total of 0.9%, 3.5%, and 2.6% of patients discontinued, reduced, or interrupted mobocertinib due to an event of rash.

Palmar-plantar erythrodysaesthesia (PPE) is a known risk of tyrosine kinase inhibitors (TKIs), more commonly with multi-kinase inhibitors. All-grade TEAEs of PPE occurred in 3-4% of patients across safety populations. Of the 9 patients with PPE events in the pooled safety population (n=256), 89% were Grades 1-2 and none were serious. PPE is included in product labeling as a clinically relevant adverse reaction occurring in <10% of patients in the primary safety population.

Paronychia is a known risk of EGFR TKIs. All-grade TEAEs of the grouped term paronychia (including preferred terms paronychia, onychoclasis, nail disorder, onycholysis, onychalgia, nail infection, onychomycosis, onychomadesis, nail bed tenderness, nail discoloration and ingrowing nail) occurred in 32% of patients in the pooled safety population (n=256). All events except for one were Grade 1 or 2.

Other skin disorders were common, including dry skin in 30% of patients, pruritis in 18% and alopecia in 14%. All TEAEs were low grade and non-serious except one grade 3 event of pruritis; none required discontinuation except one grade 1 event of alopecia.

Ocular Toxicities

FDA performed a detailed review of eye disorders because ocular events, including conjunctival hyperemia, corneal opacity, discharge, thinning and/or atrophy of the corneal epithelium, were observed in non-clinical studies of mobocertinib.

In the pooled safety population (n=256), 38 patients (15%) had TEAEs within the SOC of eye disorders. The events are summarized below and were predominantly low-grade.

Upon review of the narratives, 13 patients had eye disorder TEAEs (preferred terms blindness unilateral, vision blurred, visual impairment, lacrimation increased, ocular hyperemia, diplopia, eyelid ptosis, cataract) that were attributable to other causes, including brain metastases or leptomeningeal disease, vasovagal reaction, hypertensive episode, allergic rhinitis, fungal infection, baseline vitreous degeneration or cataracts.

One patient with an eye disorder TEAE required discontinuation of mobocertinib:

- Subject AP32788-15-101-(b) (6): 71-year-old female who developed Grade 1 events of increased lacrimation, eye discharge and blurry vision starting approximately 2 weeks after initiating mobocertinib. The investigator assessed the events as probably related to mobocertinib and mobocertinib was discontinued. The events did not resolve.

The remaining 24 patients had the following Grade 1 or 2 ocular toxicities and none required dose modification:

- Thirteen patients (5%) had TEAEs of dry eye, eye pruritis or abnormal sensation in the eye
- Five patients (2%) had TEAEs of eyelid inflammation (preferred terms blepharitis, trichiasis, and chalazion)
- Two patients (1%) had TEAEs of vitreous floaters
- One patient each had TEAEs of acute angle closure glaucoma, corneal edema, conjunctival hemorrhage, and blurry vision in the setting of no other ocular symptoms.

Overall, the FDA assessed the events of ocular toxicities to be primarily low-grade and one-third were attributable to causes other than mobocertinib; however given the evidence of ocular toxicity in non-clinical studies and from clinical studies of other in-class drugs, FDA considers ocular toxicity a clinically relevant adverse event.

8.2.4.6 Treatment-Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

The rates of TEAEs (≥10% of patients) in the Pooled Prior Platinum Population were consistent with the additional 2 safety analysis populations (Table 43). The most common TEAEs were gastrointestinal (GI) disorders (the most frequently reported events in this System Organ Class (SOC) included diarrhoea, nausea, and vomiting). Skin and subcutaneous tissue disorders was the second most common SOC for each of the 3 safety analysis populations, with rash and dry skin being the most frequently reported PTs.

Table 43: Most Common (Reported in ≥10% Patients in Any Group) TEAEs by SOC and PT (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
SOC	**Pooled Prior Platinum N = 114**	**160 mg QD N = 256**	**Overall N = 325**
PT	**n (%) of Patients**		
Patients with any TEAE	**114 (100)**	**255 (100)**	**322 (99)**
Gastrointestinal disorders	**110 (96)**	**249 (97)**	**309 (95)**
Diarrhoea	105 (92)	238 (93)	291 (90)
Nausea	42 (37)	116 (45)	145 (45)
Vomiting	46 (40)	94 (37)	109 (34)
Stomatitis	27 (24)	69 (27)	80 (25)

Table 43: Most Common (Reported in ≥10% Patients in Any Group) TEAEs by SOC and PT (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
SOC	**Pooled Prior Platinum N = 114**	**160 mg QD N = 256**	**Overall N = 325**
PT	**n (%) of Patients**		
Gastrooesophageal reflux disease	17 (15)	37 (14)	50 (15)
Dry mouth	7 (6)	26 (10)	31 (10)
Dyspepsia	12 (11)	25 (10)	29 (9)
Mouth ulceration	14 (12)	15 (6)	15 (5)
Skin and subcutaneous tissue disorders	**102 (89)**	**211 (82)**	**254 (78)**
Rash	51 (45)	96 (38)	109 (34)
Dry skin	37 (32)	75 (29)	92 (28)
Dermatitis acneiform	22 (19)	49 (19)	56 (17)
Rash maculopapular	15 (13)	38 (15)	49 (15)
Pruritus	27 (24)	45 (18)	48 (15)
Alopecia	22 (19)	36 (14)	40 (12)
Investigations	**76 (67)**	**164 (64)**	**196 (60)**
Blood creatinine increased	37 (32)	73 (29)	80 (25)
Amylase increased	25 (22)	51 (20)	64 (20)
Weight decreased	24 (21)	46 (18)	56 (17)
Lipase increased	21 (18)	39 (15)	46 (14)
Aspartate aminotransferase increased	13 (11)	35 (14)	39 (12)
Lymphocyte count decreased	7 (6)	29 (11)	35 (11)
Alanine aminotransferase increased	11 (10)	28 (11)	33 (10)
Metabolism and nutrition disorders	**65 (57)**	**150 (59)**	**192 (59)**
Decreased appetite	44 (39)	84 (33)	110 (34)
Dehydration	10 (9)	30 (12)	40 (12)
Hypomagnesaemia	14 (12)	31 (12)	40 (12)
Hypokalaemia	15 (13)	33 (13)	36 (11)
Respiratory, thoracic, and mediastinal disorders	**67 (59)**	**138 (54)**	**182 (56)**
Dyspnoea	15 (13)	41 (16)	58 (18)
Cough	24 (21)	37 (14)	49 (15)
Rhinorrhoea	15 (13)	26 (10)	27 (8)
General disorders and administration site conditions	**58 (51)**	**138 (54)**	**178 (55)**
Fatigue	21 (18)	64 (25)	84 (26)
Asthenia	13 (11)	19 (7)	27 (8)
Infections and infestations	**66 (58)**	**138 (54)**	**171 (53)**

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Table 43: Most Common (Reported in ≥10% Patients in Any Group) TEAEs by SOC and PT (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
SOC	**Pooled Prior Platinum N = 114**	**160 mg QD N = 256**	**Overall N = 325**
PT	**n (%) of Patients**		
Paronychia	40 (35)	69 (27)	76 (23)
Nervous system disorders	**34 (30)**	**98 (38)**	**125 (38)**
Headache	11 (10)	35 (14)	43 (13)
Musculoskeletal and connective tissue disorders	**46 (40)**	**91 (36)**	**117 (36)**
Back pain	24 (21)	32 (13)	43 (13)
Blood and lymphatic system disorders	**47 (41)**	**93 (36)**	**109 (34)**
Anaemia	36 (32)	71 (28)	85 (26)
Vascular disorders	**15 (13)**	**43 (17)**	**57 (18)**
Hypertension	10 (9)	29 (11)	33 (10)

Source: Module 2.7.4 Table 18.1.1.13.1. Data cutoff: 29 May 2020.

AE: adverse event; PT: Preferred Term; QD: once daily; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

TEAEs are defined as any AE that occurs from the first dose of study drug and through the end of treatment until 30 days after the last dose of study drug. A patient reporting the same event more than once has that event counted only once within each SOC, and once within each PT. MedDRA Dictionary (Version 23.0) was used for coding adverse events.

The FDA's Assessment:

In the primary safety population (n=114), the most common (≥10%) TEAEs observed in patients enrolled in Study 101 are provided in Table 44. Discrepancies between the FDA's and the Applicant's assessments are due to differences in grouping of preferred terms.

Table 44: Adverse reactions occurring in ≥ 10% of patients in the primary safety population of Study 101

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Adverse Reaction	EXKIVITY (N = 114)	
	All Grades* (%)	Grade 3 or 4 (%)
Gastrointestinal Disorders		
Diarrhea	92	22
Stomatitis[a]	46	4.4**
Vomiting	40	2.6**
Decreased appetite	39	0.9**
Nausea	37	4.4**
Decreased weight	21	0
Abdominal pain[b]	18	1.8**
Gastroesophageal reflux disease	15	0
Dyspepsia	11	0
Skin and Subcutaneous Tissue Disorders		
Rash[c]	78	1.8**
Paronychia[d]	39	0.9**
Dry skin	32	0
Pruritus	24	0.9**
Alopecia	19	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[e]	34	2.6**
General Disorders and Administration Site Conditions		
Fatigue[f]	29	3.5**
Respiratory, Thoracic and Mediastinal Disorders		
Cough[g]	24	0
Upper respiratory tract infection[h]	16	0
Dyspnea[i]	15	4.4
Rhinorrhea	13	0
Eye Disorders		
Ocular Toxicity[j]	11	0

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Cardiac Disorders		
QTc interval prolongation[k]	10	3.5
Hypertension[l]	10	4.4**
Nervous System Disorders		
Headache	10	0

* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5)

** Events of Grade 3 only (no Grade 4 occurred)

[a] Stomatitis includes angular cheilitis, aphthous ulcer, cheilitis, mouth ulceration, mucosal inflammation, odynophagia, and stomatitis.

[b] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.

[c] Rash includes acne, dermatitis, dermatitis acneiform, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, and urticaria.

[d] Paronychia includes nail bed tenderness, nail disorder, nail infection, onycholysis, and paronychia.

[e] Musculoskeletal pain includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.

[f] Fatigue includes asthenia, and fatigue.

[g] Cough includes cough, productive cough, and upper-airway cough syndrome.

[h] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, and upper respiratory tract infection.

[i] Dyspnea includes dyspnea, and dyspnea exertional.

[j] Ocular toxicity includes dry eye, eye pruritis, abnormal sensation in eye, eye discharge, blepharitis, trichiasis, conjunctival hemorrhage, vitreous floaters, blurred vision and corneal edema.

[k] QTc interval prolongation includes electrocardiogram QT prolonged, and ventricular arrhythmia.

[l] Hypertension includes blood pressure increased, and hypertension.

Clinically relevant adverse reactions in <10% of patients in the primary safety population included edema (9%), acute kidney injury (8%), peripheral neuropathy (7%), palmar-plantar erythrodysaesthesia (4.4%), pneumonitis (2.6%) and cardiac failure (2.6%).

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In the pooled safety population (n=256), the most common (≥10%) TEAEs included the same events with similar rates of occurrence, in addition to dehydration (12%), peripheral neuropathy (11%) and dry mouth (10%).

8.2.4.7 TRAEs

The Applicant's Position:

All 3 safety populations received single-agent mobocertinib; therefore, the majority of TEAEs were reported as related to study drug. Generally, the TRAEs were comparable across all 3 safety populations, as outlined in Table 45. The most common TRAEs (≥10% of patients in any group) were from SOC GI disorders (diarrhoea, nausea, and vomiting) and skin and subcutaneous tissue disorders (rash and dry skin).

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Table 45: Most Common (Reported in ≥10% of Patients in Any Group) Drug-Related TEAEs by SOC and PT (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib		
SOC	Pooled Prior Platinum N = 114	160 mg QD N = 256	Overall N = 325
PT	n (%) of Patients		
Patients with any drug-related TEAE	**113 (99)**	**252 (98)**	**315 (97)**
Gastrointestinal disorders	**107 (94)**	**242 (95)**	**295 (91)**
Diarrhoea	103 (90)	233 (91)	280 (86)
Nausea	37 (32)	100 (39)	118 (36)
Vomiting	34 (30)	71 (28)	82 (25)
Stomatitis	25 (22)	65 (25)	74 (23)
Gastrooesophageal reflux disease	14 (12)	31 (12)	37 (11)
Mouth ulceration	14 (12)	14 (5)	14 (4)
Skin and subcutaneous tissue disorders	**101 (89)**	**206 (80)**	**241 (74)**
Rash	51 (45)	94 (37)	104 (32)
Dry skin	34 (30)	69 (27)	83 (26)
Dermatitis acneiform	21 (18)	48 (19)	55 (17)
Rash maculopapular	15 (13)	38 (15)	49 (15)
Pruritus	23 (20)	38 (15)	41 (13)
Alopecia	17 (15)	27 (11)	31 (10)
Investigations	**58 (51)**	**123 (48)**	**141 (43)**
Blood creatinine increased	28 (25)	45 (18)	46 (14)
Amylase increased	19 (17)	38 (15)	45 (14)
Lipase increased	21 (18)	35 (14)	40 (12)
Weight decreased	12 (11)	26 (10)	32 (10)
Metabolism and nutrition disorders	**49 (43)**	**105 (41)**	**127 (39)**
Decreased appetite	37 (32)	66 (26)	84 (26)
General disorders and administration site conditions	**38 (33)**	**93 (36)**	**112 (34)**
Fatigue	15 (13)	47 (18)	62 (19)
Infections and infestations	**45 (39)**	**91 (36)**	**102 (31)**
Paronychia	39 (34)	68 (27)	75 (23)
Blood and lymphatic system disorders	**27 (24)**	**58 (23)**	**63 (19)**
Anaemia	19 (17)	41 (16)	44 (14)

Source: Module 2.7.4 Table 18.1.1.13.2. Data cutoff: 29 May 2020.

AE: adverse event; PT: Preferred Term; QD: once daily; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

TEAEs are defined as any AE that occurs from the first dose of study drug and through the end of treatment until 30 days after the last dose of study drug. A patient reporting the same event more than once has that event counted only once within each SOC, and once within each PT.

The FDA's Assessment:

The FDA did not independently verify the TEAEs reported to be treatment-related as attribution of AEs is difficult to assess in non-randomized trials without a control arm.

8.2.4.8 TEAEs Grade ≥3

The Applicant's Position:

The majority of TEAEs in the Pooled Prior Platinum Safety Population were Grade 1 or 2 events, which was consistent with 160 mg QD Population and the Overall Study Population. Most Grade ≥3 TEAEs across the 3 safety populations were of Grade 3 in severity, with Grade 3 diarrhoea being the most frequently reported event (Table 46).

In addition to diarrhoea, other frequently reported Grade ≥3 TEAEs in the Pooled Prior Platinum Safety Population (by Medical Dictionary for Regulatory Activities [MedDRA] PT) were Grade 3 anaemia, dyspnoea, hypertension, pneumonia, lipase increased, stomatitis, nausea, hypokalaemia, blood creatinine increased, renal function analyses, and ECG QT prolonged (each at least 4% each). In the 160 mg QD Population, the most frequently reported Grade 3 TEAEs in addition to diarrhoea (20%) were Grade 3 anaemia and hypertension (5% each), dyspnoea, lipase increased, and stomatitis (4% each). Anaemia (6%), hypertension (5%), and dyspnoea (4%) were also common Grade ≥3 TEAEs for the Overall Safety Population. Overall, Grade 4 TEAEs occurred in 7% to 8% in each of the 3 safety populations, however there were no individual Grade 4 events that occurred in >1% of patients in any of the 3 safety populations. The majority of the Grade 5 TEAEs (Section 8.2.4.1) across all 3 safety populations were consistent with the disease under study.

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Table 46: TEAEs Grade ≥3 (Reported in ≥5 Patients Within a Safety Population) (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib								
	Pooled Prior Platinum N = 114			160 mg QD N = 256			Overall N = 325		
	n (%) of Patients								
SOC PT	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Patients with at least 1 TEAE	**54 (47)**	**9 (8)**	**12 (11)**	121 (47)	18 (7)	27 (11)	147 (45)	22 (7)	41 (13)
Diarrhoea	24 (21)	1 (<1)	0	50 (20)	1 (<1)	0	56 (17)	1 (<1)	0
Anaemia	6 (5)	0	0	14 (5)	0	0	18 (6)	0	0
Dyspnoea	4 (4)	1 (<1)	1 (<1)	9 (4)	3 (1)	1 (<1)	14 (4)	3 (<1)	1 (<1)
Hypertension	5 (4)	0	0	14 (5)	0	0	15 (5)	0	0
Pneumonia	4 (4)	0	0	7 (3)	1 (<1)	3 (1)	10 (3)	2 (<1)	4 (1)
Lipase increased	4 (4)	1 (<1)	0	9 (4)	2 (<1)	0	10 (3)	2 (<1)	0
Amylase increased	3 (3)	1 (<1)	0	7 (3)	1 (<1)	0	11 (3)	1 (<1)	0
Stomatitis	5 (4)	0	0	9 (4)	0	0	10 (3)	0	0
Lymphocyte count decreased	3 (3)	0	0	8 (3)	0	0	9 (3)	2 (<1)	0
Nausea	5 (4)	0	0	8 (3)	0	0	10 (3)	0	0
Hyponatraemia	2 (2)	0	0	7 (3)	0	0	11 (3)	0	0
Dehydration	2 (2)	0	0	7 (3)	0	0	10 (3)	0	0
Hypokalaemia	4 (4)	0	0	7 (3)	0	0	7 (2)	0	0
Blood creatinine increased	5 (4)	0	0	5 (2)	1 (<1)	0	5 (2)	1 (<1)	0
ECG QT prolonged	4 (4)	0	0	5 (2)	0	0	6 (2)	0	0
Acute kidney injury	2 (2)	0	0	6 (2)	0	0	6 (2)	0	0
Hypoxia	1 (<1)	0	1 (<1)	5 (2)	0	1 (<1)	7 (2)	0	1 (<1)
Vomiting	3 (3)	0	0	6 (2)	0	0	7 (2)	0	0
Fatigue	3 (3)	0	0	5 (2)	0	0	6 (2)	0	0
Pericardial effusion	2 (2)	1 (<1)	0	4 (2)	1 (<1)	0	4 (1)	1 (<1)	0
Hypophosphataemia	2 (2)	0	0	5 (2)	0	0	7 (2)	0	0
NSCLC	0	0	2 (2)	0	0	4 (2)	0	0	6 (2)
Respiratory failure	0	0	1 (<1)	0	1 (<1)	3 (1)	0	2 (<1)	5 (2)
ALT increase	1 (<1)	0	0	3 (1)	1 (<1)	0	4 (1)	1 (<1)	0

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Table 46: TEAEs Grade ≥3 (Reported in ≥5 Patients Within a Safety Population) (All Analysis Populations; Data Cutoff 29 May 2020)

	Mobocertinib								
	Pooled Prior Platinum N = 114			160 mg QD N = 256			Overall N = 325		
	n (%) of Patients								
SOC PT	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Neoplasm progression	0	0	1 (<1)	0	1 (<1)	2 (<1)	0	1 (<1)	7 (2)
Pulmonary embolism	1 (<1)	0	0	4 (2)	0	0	6 (2)	0	0
Abdominal pain	2 (2)	0	0	3 (1)	0	0	5 (2)	0	0
Asthenia	1 (<1)	0	0	2 (<1)	0	0	6 (2)	0	0

Source: Module 2.7.4 18.1.1.14.1B, 18.1.1.14.1C, 18.1.1.14.1D. Data cutoff: 29 May 2020.

AE: adverse event' ALT: alanine aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; ECG: electrocardiogram; HLT: high-level term; MedDRA: Medical Dictionary for Regulatory Activities; NSCLC: non-small cell lung cancer; PT: Preferred Term; QD: once daily; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

TEAEs are defined as any AE that occurs from the first dose of study drug and through the end of treatment until 30 days after the last dose of study drug. A patient reporting the same event more than once has that event counted only once within each SOC, and once within each PT. A patient reporting the same event more than once has that event counted only once within each SOC, once within each HLT, and once within each PT. MedDRA Dictionary (Version 23.0) was used for coding adverse events. A patient counts once for the highest CTCAE within each PT, once within each HLT, and once within each SOC.

The FDA's Assessment:

Grade 3 or 4 TEAEs occurred in 55% of patients in the primary safety population (n=114). The FDA agrees that the most common severe (Grade 3 or 4) TEAE was diarrhea; 22% of patients had Grade 3 or 4 diarrhea (see Section 8.2.4.5). Other Grade 3 or 4 TEAEs that occurred in ≥2% of patients included stomatitis (4.4%), nausea (4.4%), dyspnea (4.4%), hypertension (4.4%), pneumonia (3.5%), fatigue (3.5%), acute kidney injury (3.5%), QTc prolongation (3.5%), vomiting (2.6%), pleural effusion (2.6%), musculoskeletal pain (2.6%) and pericardial effusion (2.6%).

In the pooled safety population (n=256), the most common Grade 3 or 4 TEAEs included the same events with similar rates of occurrence, and also included hypoxia (2%), dehydration (2.7%) and rash (3.1%).

While FDA agrees that no individual Grade 4 TEAEs occurred in >1% of patients, Grade 4 events of respiratory failure, hypoxia and dyspnea combined occurred in 3.1% of patients in the pooled safety population (n=256). The narratives for these events were reviewed independently and determined to be consistent with progressive disease or infectious pneumonia and not with drug-

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related ILD/pneumonitis, except for three cases of likely pneumonitis that evolved to Grade 5 events of respiratory failure as described in Section 8.2.4.1.

8.2.4.9 Laboratory Findings

The Applicant's Position:

8.2.4.9.1 Clinical Chemistry

The majority of patients in any of the 3 safety populations experienced no shift from baseline to the worst value or a shift of ≤2 grades in clinical chemistry during the study.

8.2.4.9.2 Hematology

The majority of patients in any of the 3 safety populations experienced no shift from baseline to the worst value or a shift of ≤2 grades in hematology during the study.

8.2.4.9.3 Laboratory Abnormalities

The patient incidence of potentially clinically significant laboratory abnormalities by CTCAE grade is summarized for all 3 safety analysis populations in Table 47.

Table 47: Patient Incidence of Potentially Clinically Significant (Grade ≥3) Laboratory Abnormality by NCI-CTCAE Grade (All Analysis Populations; Data Cutoff 29 May 2020)

	Pooled Prior Platinum N = 114		**160 mg QD N = 256**		**Overall N = 325**	
n (%) of patients	Baseline[a]	Post-Baseline[b]	Baseline[a]	Post-Baseline[b]	Baseline[a]	Post-Baseline[b]
Basic Metabolic Profile						
BUN	0	0	0	0	0	0
Creatinine	0	3 (3)	0	7 (3)	0	7 (2)
Phosphate	0	0	0	0	0	0
Potassium (high)	0	0	0	1 (<1)	1 (<1)	1 (<1)
Potassium (low)	0	6 (5)	2 (<1)	12 (5)	2 (<1)	12 (4)
Glucose (high)	0	0	1 (<1)	0	1 (<1)	0
Glucose (low)	0	0	0	0	0	2 (<1)
Calcium (high)	0	0	0	0	0	0
Calcium (low)	0	0	0	0	0	0
Sodium (high)	0	0	0	0	0	0
Sodium (low)	0	1 (<1)	0	2 (<1)	1 (<1)	4 (1)
Magnesium (high)	0	0	0	2 (<1)	0	2 (<1)
Magnesium (low)	0	3 (3)	0	5 (2)	0	5 (2)
Amylase (high)	2 (2)	14 (12)	4 (2)	23 (9)	4 (1)	29 (9)
Amylase (low)	0	0	0	0	0	0

Table 47: Patient Incidence of Potentially Clinically Significant (Grade ≥3) Laboratory Abnormality by NCI-CTCAE Grade (All Analysis Populations; Data Cutoff 29 May 2020)

	Pooled Prior Platinum N = 114		160 mg QD N = 256		Overall N = 325	
n (%) of patients	Baseline[a]	Post-Baseline[b]	Baseline[a]	Post-Baseline[b]	Baseline[a]	Post-Baseline[b]
Lipase (high)	1 (<1)	11 (10)	2 (<1)	22 (9)	3 (<1)	24 (7)
Lipase (low)	0	0	0	0	0	0
Liver Panel Profile						
ALP	0	2 (2)	0	3 (1)	0	3 (<1)
Total bilirubin	0	1 (<1)	1 (<1)	4 (2)	1 (<1)	4 (1)
AST	0	2 (2)	0	3 (1)	0	3 (<1)
ALT	0	3 (3)	0	4 (2)	1 (<1)	5 (2)
Hematologic Profile						
Hemoglobin	0	4 (4)	0	10 (4)	0	12 (4)
Platelet count	0	1 (<1)	0	3 (1)	0	4 (1)
ANC	0	1 (<1)	0	2 (<1)	0	2 (<1)
WBC	0	0	0	0	0	0

Source: Module 2.7.4 Table 18.1.1.22.1. Data cutoff: 29 May 2020.

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CTCAE: Common Terminology Criteria for Adverse Events; NCI: National Cancer Institute; PT: Preferred Term; QD: once daily; WBC: white blood cell count.

Significant laboratory abnormalities are defined as all Grade 3 and above abnormalities as assessed by current CTCAE version.

[a] Baseline is defined as the last observed measurement prior to or on the first dose of study drug.

[b] Post-baseline results are based on all post-baseline assessment prior to or on the last visit conducted 30 days after the last dose of the study drug regimen.

The FDA's Assessment:

The FDA's assessment of laboratory abnormalities focused on those which worsened from baseline, as summarized in Table 48 below.

Table 48: Select laboratory abnormalities worsening from baseline in ≥ 20% of patients enrolled in the primary safety population of Study 101 (FDA table)

Laboratory Abnormality	Primary safety population* (N = 114)	
	All Grades*	Grade 3 or Grade 4
Hematology		
Decreased red blood cells	59	3.5
Decreased lymphocytes	52	15
Decreased platelets	26	0.9

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Decreased leukocytes	25	0
Chemistry		
Increased creatinine	52	2.7
Increased amylase	40	13
Increased lipase	35	10
Decreased potassium	29	5.3
Increased alkaline phosphatase	25	1.8
Decreased albumin	23	1.8
Decreased magnesium	23	2.7
Increased alanine aminotransferase	22	2.7
Increased aspartate aminotransferase	21	1.8
Decreased sodium	20	0.9

* The denominator used to calculate the rate varied from 93 to 113 based on the number of patients with a baseline and at least one post-treatment value. The laboratory abnormalities are values that reflect worsening from baseline.

8.2.4.9.4 Liver Injury

Overall, hepatic laboratory values were mostly Grade 1 or 2 and outside the range for Hy's Law. One patient in the Study 101 Part 3 experienced laboratory levels on Study Day 57 that were consistent with Hy's Law (ALT >3 times the ULN; 245-323 U/L [reference range: 21 to 72 U/L]; alkaline phosphatase <2 times the ULN; 56-161 U/L [reference range: 38 to 126 U/L]; bilirubin ≥2 times the ULN; 47-60 µmol/L [reference range: 3-22 µmol/L]), potentially indicative of drug induced liver injury. However, the patient was reported to have a concurrent condition of hepatic steatosis, liver metastasis, concurrent Grade 1 GGT prior therapies that included pembrolizumab, and concurrent prolonged GI TEAEs (Grade 1 to 2 TEAEs of diarrhoea, nausea, and vomiting) and Grade 2 dehydration; and therefore, based on the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, this report did not qualify as meeting the criteria for Hy's Law. The TEAEs were deemed related to study dosing and led to dose interruption and a decrease of study dosing to 120 mg, and later resolved while the patient remained on study.

<u>The FDA's Assessment:</u>

In the pooled safety population (n=256), liver function tests worsening from baseline included increased alkaline phosphatase (23% of patients), increased alanine aminotransferase (18% of patients) and increased aspartate aminotransferase (18% of patients). Grade 3 or 4 TEAEs occurred in 1-2% of patients.

In addition, 6 patients (2.3%) had TEAEs of abnormal hepatic function, increased liver function test, liver disorder or hepatitis. Four patients had Grade 1 or 2 events. One patient had Grade 3

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non-serious liver disorder; one patient had a Grade 4 serious adverse event of hepatitis; there were no fatalities due to hepatotoxicity.

Two SAEs of hepatotoxicity include:

- Subject TAK78801-788101 (b) (6): 57-year-old female who was hospitalized for **Grade 4 hepatitis** with Grade 4 alanine aminotransferase increased, Grade 3 aspartate aminotransferase increased, and Grade 1 bilirubin increased after receiving treatment with mobocertinib for 1 month and 25 days. Mobocertinib was interrupted and subsequently dose reduced. She was also treated with steroids and the event resolved. She continued on treatment for approximately 5 months. Previous concomitant medications included minocycline hydrochloride for rash from Study Days 12 to 19. The event was attributed as not related to mobocertinib and attributed to the co-administration of minocycline; however, the FDA could not definitively rule out a contributory effect of mobocertinib to the event of hepatitis, however, the laboratory abnormalities were not consistent with Hy's law criteria.
- Subject TAK78801-788101 (b) (6): 39-year-old male who had normal liver function tests at baseline. After receiving mobocertinib for approximately 2 months, he was hospitalized for **Grade 2 increased alanine aminotransferase** and **grade 2 increased bilirubin**. On Study Day 57 his labs met criteria for Hy's law with increased ALT (maximum 323 U/L, 4.5 times the upper limit of normal), increased AST (maximum 151 U/L, 2.6 times the upper limit of normal) and increased bilirubin (maximum 60 µmol/L, 2.7 times the upper limit of normal) with normal ALP (98 U/L). An abdominal ultrasound showed mild hepatic steatosis and known liver metastases. Mobocertinib was interrupted and he was treated with IV fluids and anti-emetics. He was discharged two days later and the event resolved. He was restarted on mobocertinib at a reduced dose (120 mg) and did not have any further events that met criteria for Hy's law.

FDA agrees with the Applicant's assessment that in the pooled safety population (n=256), there was one patient with laboratory abnormalities consistent with Hy's law and potentially indicative of drug-induced liver injury (Subject TAK78801-788101- (b) (6)); however, due to the patient's underlying liver metastases, this event is unlikely attributable to mobocertinib. Although the patient met lab criteria for Hy's Law, given the alternative reasons for liver injury (liver metastases, hepatic steatosis), this event did not meet criteria for Hy's Law.

8.2.4.10 Vital Signs

The Applicant's Position:

No integrated analyses of vital signs have been performed for the summary of safety. Vital sign results are presented in the individual CSRs.

The FDA's Assessment:

In the 97 of 114 patients in the primary safety population with vital signs available, the following median values and corresponding ranges for each vital sign is listed below:

- Median Systolic Blood Pressure (SBP): 127 mmHg (range 85, 186); 14 patients (14%) had SBP ≥160 mmHg at least one time during treatment
- Median Diastolic Blood Pressure (DBP): 76 mmHg (range 44, 118); 7 patients (7%) had DBP ≥100 mmHg at least one time during treatment
- Median Pulse Rate: 81 beats per minute (range 50, 132); 33 patients (34%) had pulse rate ≥100 beats per minute at least one time during treatment
- Median Respiratory Rate: 18 breaths per minute (range 11, 26)
- Median Temperature: 36.5 degrees Celsius (range 35, 39.8); 2 patients had temperature ≥38.0 degrees Celsius
- Median Weight: 64 kilograms (range 37.3, 112.4)

8.2.4.11 Electrocardiograms (ECGs)

The Applicant's Position:

No integrated analyses of ECGs have been performed for the summary of safety. ECG results are presented in the individual study CSRs.

In the Pooled Prior Platinum Population ventricular rates were within the reference range at the time of each assessment (50-120 bpm). Eleven (10%) patients experienced a TEAE of QT prolongation; 8 patients had events that were deemed related to study dosing and 4 patients experienced an event that was Grade ≥3. None of these events lead to discontinuation of study dosing. However, there was 1 SAE of ventricular arrhythmia associated with Torsades de Pointes that occurred in Study 101 Part 3 (Section 8.2.4.5 under the cardiac disorders AECI).

A concentration-dependent QTcF interval prolongation of approximately 12.7 msec (90% CI: 8.69, 16.8) was observed at the steady-state C_{max} after160 mg QD mobocertinib doses based on an analysis of data from 194 patients with advanced malignances (Section 6.3.1).

The FDA's Assessment:

In the 250-patient subset of the pooled safety population (n=256) who had scheduled and unscheduled electrocardiograms (ECGs), 1.2% of patients had a QTc interval > 500 msec and 11% of patients had a change-from-baseline QTc interval > 60 msec. Torsades de Pointes

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occurred in 1 patient (0.4%). Refer to the Interdisciplinary Review Team for Cardiac Safety Studies QT Study Review for complete details of the ECG analyses.

8.2.5 Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Not applicable.

The FDA's Assessment:

See Section 8.2.4.5.

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

The Applicant's Position:

In Study 101 PRO were assessed using health-related quality of life (HRQOL). Results for PRO are presented in Section 8.1.2.1.7.

The FDA's Assessment:

See Section 8.1.2.1.7.

8.2.7 Safety Analyses by Demographic Subgroups

For all 3 analysis populations, the incidence of TEAEs by SOC and PT are presented by intrinsic (ie, age, sex, race) and extrinsic (region) factors.

8.2.7.1 Intrinsic Factors

8.2.7.1.1 TEAEs by Age

The Applicant's Position:

In the Pooled Prior Platinum Population, the most common TEAEs in patients aged 18 to <65 years of age were diarrhoea (93%), rash (49%), vomiting (46%), paronychia (40%), nausea (36%), decreased appetite (32%), dry skin (32%), anaemia (29%), and blood creatinine increased (29%). The most common TEAEs in patients aged ≥65 years were diarrhoea (90%), decreased appetite (50%), rash (38%), nausea (38%), blood creatinine increased (38%), anaemia (36%), dry skin (33%), amylase increased (31%), and vomiting (31%).

Similar patterns were observed for the 160 mg QD and Overall Safety Populations.

The FDA's Assessment:

Of the 114 patients in the primary safety population, 37% were 65 years and over and 7% were 75 years and over. An exploratory analysis of the difference in incidence of TEAEs by age group suggests a higher incidence of grade 3 and 4 TEAEs (69% vs. 47%) and serious TEAEs (64% vs. 35%) in patients 65 years and older as compared to those younger than 65 years. These

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differences appear to be mostly driven by an increased number of high-grade and serious TEAEs of diarrhea and acute kidney injury in older patients.

8.2.7.1.2 TEAEs by Sex

The Applicant's Position:

In Pooled Prior Platinum Population, the majority of patients were female. The most common TEAEs in female patients were diarrhoea (93%), vomiting (47%), rash (40%), decreased appetite (39%), nausea (36%), and paronychia (35%), blood creatinine increased (31%), and anaemia (31%). In male patients, the most common TEAEs were diarrhoea (90%), rash (54%), decreased appetite (38%), dry skin (38%), nausea (38%), blood creatinine increased (36%), paronychia (36%), and anaemia (33%).

Similar patterns were observed for the 160 mg QD and Overall Safety Populations.

The FDA's Assessment:

In the pooled safety population (n=256), there were more females (n=169) than males (n=87), as previously described. The incidence of specific all-grade TEAEs by sex that differed by >10% included vomiting (43% in females vs. 24% in males), rash (68% in females vs. 83% in males), musculoskeletal pain (33% in females vs. 20% in males), stomatitis (47% in in females vs. 36% in males), alopecia (18% in females vs. 7% in males) and headache (18% in females vs. 7% in males). Grade 3 or 4 TEAEs were more common in females (59%) than males (45%), with diarrhea as the one high-grade TEAE that differed by >5% (25% in females vs. 10% in males). The incidence of SAEs by sex did not differ by more than 5%. However, due to the small numbers of patients in each subgroup, it is not possible to draw definitive conclusions on whether there are differences in the safety profile of mobocertinib by sex.

8.2.7.1.3 TEAEs by Race

The Applicant's Position:

In the Pooled Prior Platinum Population, the majority of patients were Asian. The most common TEAEs in Asian patients were diarrhoea (91%), rash (49%), paronychia (46%), anaemia (35%), blood creatinine increased (35%), dry skin (35%), vomiting (35%), and decreased appetite (32%), and nausea (31%). The most common TEAEs in non-Asian patients were diarrhoea (93%), vomiting (47%), decreased appetite (47%), nausea (44%), rash (38%), blood creatinine increased (29%), dry skin (29%), and pruritus (29%).

Similar patterns were observed for the 160 mg QD and Overall Safety Populations.

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The FDA's Assessment:

In the pooled safety population (n=256), 139 patients (54%) were White, 102 patients (40%) were Asian, 12 patients (5%) were Black or African American and 3 patients (1%) did not have an identified race. The incidence of specific all grade TEAEs that were >10% more common in Asians than Whites included stomatitis (58% vs. 35%), dry skin (37% vs. 23%), increased amylase (30% vs. 12%), increased lipase (23% vs. 9%) and paronychia (43% vs. 18%). The incidence of specific all grade TEAEs that were >10% more common in Whites than Asians included nausea (49% vs. 36%), dehydration (16% vs. 3%) and fatigue (36% vs. 21%). Individual grade 3 or 4 TEAEs or SAEs did not differ by >10%. However, due to the small numbers of patients in each subgroup, it is not possible to draw definitive conclusions on whether there are differences in the safety profile of mobocertinib by race. The Applicant will conduct an analysis containing data from clinical trials enrolling a sufficient representation of U.S. racial and ethnic minorities, including Black or African American patients, to further characterize the safety and efficacy of mobocertinib in Black or African American patients with EGFR exon 20 insertion mutated NSCLC. Extrinsic Factors

8.2.7.1.4 Region

The Applicant's Position:

For patients in the Pooled Prior Platinum Population, approximately half were from Asia (n = 55) and the other half from the combination of North America and Europe (n = 59). In the Pooled Prior Platinum Population, the most common TEAEs in patients from North America + Europe were diarrhoea (92%), nausea (47%), vomiting (47%), decreased appetite (46%), rash (37%), fatigue (36%), anaemia (34%), blood creatinine increased (31%), dry skin (31%), and paronychia (31%). The most common TEAEs in patients from Asia were diarrhoea (93%), rash (53%), paronychia (40%), dry skin (35%), blood creatinine increased (35%), vomiting (33%), and decreased appetite (31%).

Similar patterns were observed for the 160 mg QD and Overall Safety Populations.

The FDA's Assessment:

Differences in TEAEs by region (e.g., North America/Europe vs. Asia) were similar to differences by race (e.g., White vs. Asian).

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:

This subsection is not applicable to this review, as no separate studies have been conducted to evaluate specific safety concerns.

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The FDA's Assessment:

8.2.9 Not applicable. Additional Safety Explorations

8.2.9.1 Human Carcinogenicity or Tumor Development

The Applicant's Position:

Not applicable

The FDA's Assessment:

8.2.9.2 Not applicable. Human Reproduction and Pregnancy

The Applicant's Position:

As of the data cutoff of 29 May 2020, no cases of pregnancy were reported in any of the safety populations and no lactating women were exposed to the study drug.

In Study TAK-788-1004, a patient's partner experienced pregnancy 5 weeks post the last dose of mobocertinib. No associated AEs were reported regarding this pregnancy.

There are no clinical data regarding the potential effect of mobocertinib on pregnancy or development of the embryo or fetus. There are no experiences with the drug having been administered to pregnant or lactating women.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.9.3 Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Mobocertinib has an orphan drug designation and is exempt from this requirement to assess safety in pediatric population.

The FDA's Assessment:

The safety of mobocertinib has not been established in pediatric patients. This application is not exempt from the requirements of PREA as amended by FDARA even though it has orphan designation; however, given the rarity of EGFR Exon 20 insertion mutations in pediatric cancers, a full waiver for the conduct of pediatric studies was requested and the FDA agrees with granting a full waiver based on the extreme rarity of these mutations.

8.2.9.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

As of 29 May 2020, there were no overdoses reported in the safety population. No specific antidote is available for overdose with mobocertinib. Treatment of overdose consists of general

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supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

The FDA's Assessment:

8.2.10 FDA agrees with the Applicant's position. Safety in the Postmarket Setting

8.2.10.1 Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable. There is no marketing experience to report for mobocertinib. Mobocertinib has not been marketed or approved in any country/territory.

The FDA's Assessment:

Not applicable.

8.2.10.2 Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Mobocertinib has a safety profile that is similar to that of the already approved EGFR TKIs, and offers a more convenient route of use and improvement for certain safety concerns when compared to immunology or chemotherapies. The TEAEs are tolerable and manageable. In conclusion, these efficacy and safety data demonstrate that mobocertinib has a favorable benefit-to-risk profile for patients with previously treated NSCLC that has *EGFR Exon 20* insertion mutations.

Together, the strong results from Part 3 of Study 101, the Pooled Prior Platinum Analysis Set, and those from Parts 1 and 2 of Study 101 support a positive benefit-risk assessment for mobocertinib when administered at a dose of 160 mg QD as a treatment for patients with *EGFR Exon 20* insertion mutation-positive metastatic NSCLC who have received prior platinum-based chemotherapy.

The risks associated with mobocertinib treatment discussed in this summary have been characterized and are manageable by recommendations included in the proposed labeling, discussed in Section 11.0.

The FDA's Assessment:

Due to the risk of QTc prolongation/Torsades de Pointes, FDA issued a post-marketing requirement (PMR) to conduct an integrated safety analysis containing data from randomized clinical trials to further characterize the known serious signal of QT prolongation, ventricular arrhythmia and Torsades de Pointes. FDA also included a boxed warning in the prescribing information to further inform prescribers and patients of the risk of QTc prolongation/Torsades de Pointes and to provide risk mitigation information.

FDA did not consider a REMS for this safety signal to be necessary to ensure the safe and effective use of mobocertinib. Mobocertinib will be prescribed by oncologists who are trained in

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how to monitor, diagnose, and manage serious adverse reactions, including QTc prolongation, 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

Data

The safety data described below reflect exposure to mobocertinib in clinical trials, at the recommended dose of 160 mg once daily in 114 patients with metastatic NSCLC with *EGFR Exon 20* insertion mutations who had previously been treated with platinum-based chemotherapy patients with a history of ILD, drug-related pneumonitis, radiation pneumonitis that required steroid treatment, or significant, uncontrolled, active cardiovascular disease, or prolonged QTc interval were excluded from enrollment in these trials. The median duration of exposure to mobocertinib was 6.97 months. Among the 114 patients who received mobocertinib, 46% were exposed for 6 months to <12 months and 14% were exposed for greater than 1 year.

The most common adverse reactions, reported by ≥25% of patients in the Pooled Prior Platinum Safety Population were diarrhoea, rash, stomatitis, vomiting, decreased appetite, nausea, dry skin, paronychia, blood creatinine increased, and anaemia (Table 49).

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Table 49: Adverse Reactions in Patients in the Pooled Prior Platinum Analysis Set

Adverse Reaction	Mobocertinib 160 mg QD (N = 114)		
	All Grades	Grade 3	Grade 4
Subjects with at Least 1 Adverse Drug Reaction	114 (100.0)	42 (36.8)	5 (4.4)
Blood and lymphatic system disorders	36 (31.6)	6 (5.3)	0
Anaemia	36 (31.6)	6 (5.3)	0
Metabolism and nutrition disorders	44 (38.6)	1 (0.9)	0
Decreased appetite	44 (38.6)	1 (0.9)	0
Cardiac disorders	13 (11.4)	4 (3.5)	2 (1.8)
Cardiac failure[a]	3 (2.6)	1 (0.9)	1 (0.9)
QT interval prolongation[b]	11 (9.6)	3 (2.6)	1 (0.9)
Respiratory, thoracic, and mediastinal disorders	2 (1.8)	1 (0.9)	0
Interstitial lung disease[c]	2 (1.8)	1 (0.9)	0
Gastrointestinal disorders	109 (95.6)	29 (25.4)	1 (0.9)
Diarrhoea	105 (92.1)	24 (21.1)	1 (0.9)
Nausea	42 (36.8)	5 (4.4)	0
Vomiting	46 (40.4)	3 (2.6)	0
Stomatitis[d]	53 (46.5)	5 (4.4)	0
Investigations	58 (50.9)	12 (10.5)	2 (1.8)
Amylase increased	25 (21.9)	3 (2.6)	1 (0.9)
Lipase increased	21 (18.4)	4 (3.5)	1 (0.9)
Aspartate aminotransferase increased	13 (11.4)	0	0
Alanine aminotransferase increased	11 (9.6)	1 (0.9)	0
Blood creatinine increased	37 (32.5)	5 (4.4)	0
Infections and infestations	40 (35.1)	1 (0.9)	0
Paronychia	40 (35.1)	1 (0.9)	0
Skin and subcutaneous tissue disorders	99 (86.8)	3 (2.6)	0
Rash[e]	94 (82.5)	3 (2.6)	0
Dry skin[f]	40 (35.1)	0	0

Source: Module 2.7.4 Table 18.1.1.25.1D. Data cutoff: 29 May 2020.
Adverse drug reaction is limited to AEs which occur after administration of the first dose of study drug and up to 30 days after the last dose of study medication. A subject counts once for the highest grade in each category. Percentages use the number of treated subjects as the denominator. AEs are graded according to NCI-CTCAE v5.0. MedDRA Dictionary (Version 23.0) was used for coding adverse events.

[a] Includes cardiac failure, cardiac failure congestive, ejection fraction decreased, cardiomyopathy. One Grade 5 event of cardiac failure was reported.

[b] Includes electrocardiogram QT prolonged, ventricular arrhythmia.

[c] Includes interstitial lung disease and pneumonitis.

[d] Includes stomatitis, mouth ulceration, aphthous ulcer, mucosal inflammation, cheilitis, angular cheilitis, odynophagia.

[e] Includes rash, rash maculopapular, rash papular, rash pruritic, rash pustular, dermatitis acneiform, pruritus, dermatitis, eczema, palmar-plantar erythrodysaesthesia syndrome, erythema, urticaria, folliculitis.

[f] Includes dry skin, skin fissures, skin exfoliation.

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Serious adverse reactions occurred in 17.5% of patients in the Pooled Prior Platinum Safety Population (Table 50; the most common serious adverse reactions (≥2%) were diarrhoea (7.9%), vomiting (4.4%), nausea (2.6%), and cardiac failure (2.6%).

Table 50: Serious Adverse Reactions in Patients in the Pooled Prior Platinum Analysis Set

Adverse Reaction	Mobocertinib 160 mg QD (N = 114)		
	All Grades	Grade 3	Grade 4
Subjects with at Least 1 Adverse Drug Reaction	20 (17.5)	10 (8.8)	3 (2.6)
Blood and lymphatic system disorders	0	0	0
Anaemia	0	0	0
Metabolism and nutrition disorders	1 (0.9)	1 (0.9)	0
Decreased appetite	1 (0.9)	1 (0.9)	0
Cardiac disorders	4 (3.5)	1 (0.9)	2 (1.8)
Cardiac failure[a]	3 (2.6)	1 (0.9)	1 (0.9)
QT interval prolongation[b]	1 (0.9)	0	1 (0.9)
Respiratory, thoracic, and mediastinal disorders	1 (0.9)	1 (0.9)	0
Interstitial lung disease[c]	1 (0.9)	1 (0.9)	0
Gastrointestinal disorders	13 (11.4)	7 (6.1)	1 (0.9)
Diarrhoea	9 (7.9)	5 (4.4)	1 (0.9)
Nausea	3 (2.6)	3 (2.6)	0
Vomiting	5 (4.4)	0	0
Stomatitis[d]	0	0	0
Investigations	2 (1.8)	1 (0.9)	0
Amylase increased	0	0	0
Lipase increased	0	0	0
Aspartate aminotransferase increased	0	0	0
Alanine aminotransferase increased	1 (0.9)	0	0
Blood creatinine increased	1 (0.9)	1 (0.9)	0
Infections and infestations	0	0	0
Paronychia	0	0	0
Skin and subcutaneous tissue disorders	0	0	0
Rash[e]	0	0	0
Dry skin[f]	0	0	0

Source: Module 2.7.4 Table 18.1.1.25.2D. Data cutoff: 29 May 2020.
Adverse drug reaction is limited to AEs which occur after administration of the first dose of study drug and up to 30 days after the last dose of study medication. A subject counts once for the highest grade in each category. Percentages use the number of treated subjects as the denominator. AEs are graded according to NCI-CTCAE v5.0. MedDRA Dictionary (Version 23.0) was used for coding adverse events.

[a] Includes cardiac failure, cardiac failure congestive, ejection fraction decreased, cardiomyopathy. One Grade 5 event of cardiac failure was reported.

[b] Includes electrocardiogram QT prolonged, ventricular arrhythmia.

[c] Includes interstitial lung disease and pneumonitis.

Table 50: Serious Adverse Reactions in Patients in the Pooled Prior Platinum Analysis Set

Adverse Reaction	Mobocertinib 160 mg QD (N = 114)		
	All Grades	Grade 3	Grade 4

[d] Includes stomatitis, mouth ulceration, aphthous ulcer, mucosal inflammation, cheilitis, angular cheilitis, odynophagia.
[e] Includes rash, rash maculopapular, rash papular, rash pruritic, rash pustular, dermatitis acneiform, pruritus, dermatitis, eczema, palmar-plantar erythrodysaesthesia syndrome, erythema, urticaria, folliculitis.
[f] Includes dry skin, skin fissures, skin exfoliation.

Adverse reactions leading to dose reductions occurred in 20.2% of patients in the Pooled Prior Platinum Safety Population. The most common adverse reactions (≥2%) leading to dose reductions were diarrhoea (9.6%), nausea (5.3%), rash (4.4%), vomiting (2.6%), and stomatitis (2.6%). Adverse reactions leading to permanent discontinuation occurred in 11.4% of patients in the Pooled Prior Platinum Analysis Set (Table 51). The most common adverse reactions (≥2%) leading to permanent discontinuation were diarrhoea (4.4%) and nausea (3.5%) (Table 51).

Table 51: Adverse Reactions Leading to Dose Reductions and Discontinuations in Patients in the Pooled Prior Platinum Analysis Set

Adverse Reaction	Mobocertinib 160 mg QD (N = 114)	
	Dose Reduction	Discontinuation
Subjects with at Least 1 Adverse Drug Reaction	23 (20.2)	13 (11.4)
Blood and lymphatic system disorders	0	0
Anaemia	0	0
Metabolism and nutrition disorders	2 (1.8)	2 (1.8)
Decreased appetite	2 (1.8)	2 (1.8)
Cardiac disorders	0	2 (1.8)
Cardiac failure[a]	0	1 (0.9)
QT interval prolongation[b]	0	1 (0.9)
Respiratory, thoracic, and mediastinal disorders	0	1 (0.9)
Interstitial lung disease[c]	0	1 (0.9)
Gastrointestinal disorders	16 (14.0)	9 (7.9)
Diarrhoea	11 (9.6)	5 (4.4)
Nausea	6 (5.3)	4 (3.5)
Vomiting	3 (2.6)	2 (1.8)
Stomatitis[d]	3 (2.6)	2 (1.8)

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Table 51: Adverse Reactions Leading to Dose Reductions and Discontinuations in Patients in the Pooled Prior Platinum Analysis Set

Adverse Reaction	Mobocertinib 160 mg QD (N = 114)	
	Dose Reduction	Discontinuation
Investigations	5 (4.4)	1 (0.9)
Amylase increased	0	1 (0.9)
Lipase increased	2 (1.8)	0
Aspartate aminotransferase increased	1 (0.9)	0
Alanine aminotransferase increased	1 (0.9)	0
Blood creatinine increased	2 (1.8)	0
Infections and infestations	2 (1.8)	0
Paronychia	2 (1.8)	0
Skin and subcutaneous tissue disorders	5 (4.4)	1 (0.9)
Rash[e]	5 (4.4)	1 (0.9)
Dry skin[f]	1 (0.9)	0

Source: Module 2.7.4 Table 18.1.1.25.3D and Table 18.1.1.25.4D. Data cutoff: 29 May 2020.
Adverse drug reaction is limited to AEs which occur after administration of the first dose of study drug and up to 30 days after the last dose of study medication. A subject counts once for the highest grade in each category. Percentages use the number of treated subjects as the denominator. AEs are graded according to NCI-CTCAE v5.0. MedDRA Dictionary (Version 23.0) was used for coding adverse events.

[a] Includes cardiac failure, cardiac failure congestive, ejection fraction decreased, cardiomyopathy.

[b] Includes electrocardiogram QT prolonged, ventricular arrhythmia.

[c] Includes interstitial lung disease and pneumonitis.

[d] Includes stomatitis, mouth ulceration, aphthous ulcer, mucosal inflammation, cheilitis, angular cheilitis, odynophagia.

[e] Includes rash, rash maculopapular, rash papular, rash pruritic, rash pustular, dermatitis acneiform, pruritus, dermatitis, eczema, palmar-plantar erythrodysaesthesia syndrome, erythema, urticaria, folliculitis.

[f] Includes dry skin, skin fissures, skin exfoliation.

The Applicant's Position:

The clinical safety data available for the Pooled Prior Platinum Safety Set as of 29 May 2020 indicates mobocertinib has an acceptable and manageable safety profile. The TEAEs are consistent and generally expected on the basis of nonclinical, early clinical studies with mobocertinib, as well as mechanism-related TEAEs [55]. Safety for mobocertinib is summarized as follows:

- The most frequently reported TEAEs were GI-related with diarrhoea being the most frequent of these events. The majority of these TEAEs were Grade 1, 2, or 3 events, and few led to dose discontinuation.
- The most frequently reported Grade ≥3 TEAEs (reported in at least 4% of patients in the Pooled Prior Platinum Safety Set) were diarrhoea, anaemia, dyspnoea, hypertension, pneumonia, nausea, hypokalaemia, blood creatinine increased, stomatitis, renal function analyses, ECG QT prolonged, and lipase increased.

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- AECI, which included GI toxicity (diarrhoea, nausea, vomiting), skin reactions, ILD (includes pneumonitis), cardiac disorders, amylase/lipase increase, and stomatitis, were monitorable and manageable.
- In addition to the primarily low-grade GI and skin effects commonly reported in the Overall Safety Population, less common, although more severe and potentially fatal events of ILD and cardiac failure were reported with mobocertinib. QT prolongation has also been reported, which has the potential to be fatal. The frequency and severity of these risks reported with mobocertinib are consistent with the class of EGFR TKIs.
- The AEs noted with mobocertinib were manageable, reversible, and generally resolved with standard symptomatic measures, dose modification and/or drug discontinuation. Results over time indicate that prolonged treatment with mobocertinib had acceptable tolerability with no evidence of cumulative toxicity.
- The safety profile is consistent in non-Asian and Asian patients, as well as across age, region, and gender.
- There were no particular safety findings that are unique to mobocertinib compared with published data of toxicity profiles of other EGFR TKIs. Mobocertinib has an improved safety profile when compared with chemotherapy and immunotherapy.
- The model-based prediction of QTcF interval change from baseline at the steady-state C_{max} after 160 mg QD mobocertinib was 12.7 msec (90% CI: 8.69, 16.8). The corresponding prediction for the JT_{peak} interval change from baseline was 11.1 msec (90% CI: 3.12, 18.9). No statistically significant relationship was identified between concentration and the RR interval, supporting the lack of a clinically meaningful effect on heart rate (Section 6.3.1).

<u>The FDA's Assessment:</u>

The FDA generally agrees with the Applicant's assessment of the safety of mobocertinib, with exceptions described in the preceding FDA sections. The FDA agreed with the Applicant's identification of the significant and serious safety signals of QTc prolongation/Torsades de Pointes, ILD/pneumonitis, cardiac toxicity, and diarrhea for inclusion in Section 5 of the proposed USPI. Given the life-threatening and potentially fatal nature of QTc prolongation and Torsades de Pointes, The FDA included a boxed warning to further describe this risk. The FDA considers the agreed-upon product labeling adequate to address safety concerns associated with the use of mobocertinib.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

Data from Study 101 were analyzed according to the pre-specified statistical analysis plan. There were no major statistical issues identified during review of the application. The estimated response rate is considered reasonably likely to predict clinical benefit when considered in the context of the durability of responses, differing safety profile from currently available therapy, and oral route of administration. The single-arm design of the study limits the assessment of long-term clinical benefit of mobocertinib based on time-to-event endpoints, such as PFS and OS.

8.4 Conclusions and Recommendations

The FDA's Assessment:

Study 101 is an international, open-label, multicohort, dose escalation and dose expansion study of 305 patients with locally advanced or metastatic NSCLC, of whom 114 patients had documented EGFR exon 20 mutations with disease progression on or after platinum-based chemotherapy and received mobocertinib at a dose of 160 mg per day. The primary efficacy outcome measure was ORR as assessed by BICR according to RECIST v1.1. The ORR observed in the primary efficacy population (n=114) was 28% (95% CI: 20, 27), the median duration of response (DOR) was 17.5 months (95% CI: 7,20), and 59% of patients had a DOR ≥6 months.

Mobocertinib has an acceptable safety profile for the intended population of patients with a life-threatening disease and few alternative treatments, including no other option for orally administered therapy. The serious adverse reactions of QTc Interval Prolongation and Torsades de Pointes, Interstitial Lung Disease (ILD)/pneumonitis, Cardiac Toxicity, and diarrhea are adequately addressed in the product labeling, which includes a boxed warning for QTc prolongation and Torsades de Pointes. In addition to the boxed warning regarding QTc prolongation and Torsades de Pointes, the Applicant will conduct an integrated analysis of QTc interval prolongation and Torsades de Pointes data and of cardiac failure data from randomized clinical trials to further characterize this identified safety signal.

Given the size of the efficacy population, the duration of the follow-up, and the single-arm nature of Study 101, we recommend accelerated approval of this application. The Applicant is conducting a multicenter, randomized clinical trial to confirm the clinical benefit of mobocertinib in patients with locally advanced or metastatic non-small cell lung cancer whose tumors harbor an EGFR exon 20 insertion mutation based on an improvement in PFS as the primary measure of efficacy. In addition, while published data suggests that patients with EGFR exon 20 insertion mutated NSCLC are more likely to be Black or African American than other patients with NSCLC (14% vs. 6%) (Choudhury, Clin Canc Res, 2021), Black or African American patients comprised only 3% of the primary efficacy population of Study 101. As a post-marketing commitment, the Applicant will submit a report of data from clinical trials enrolling a sufficient representation of Black or African American patients and other racial or ethnic minorities that is

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reflective of the US population of patients with EGFR exon 20 insertion-mutated NSCLC to further characterize the safety and efficacy of mobocertinib in these patients.

Based on a favorable benefit-risk assessment, the FDA recommends accelerated approval for mobocertinib for the following indication:

"the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy."

X _____ X _____

Anup Amatya, PhD
Primary Statistical Reviewer

Pallavi Mishra-Kalyani, PhD
Statistical Team Leader

X _____ X _____

Elizabeth Duke, MD
Liza Stapleford, MD
Primary Clinical Reviewer

Nicole Drezner, MD
Clinical Team Leader

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9.0 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

The FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

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10.0 PEDIATRICS

The Applicant's Position:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Mobocertinib received a full waiver of pediatric studies for the treatment of NSCLC and advanced solid tumors that harbor an EGFR/HER2 mutation across all pediatric age groups. The agreed initial pediatric study plan is included in the original NDA submission per 505B(a)(3)(A)(ii)(II) of the FD&C Act.

Orphan drug designation was granted on 17 December 2019 for the treatment of NSCLC with genetic alteration in EGFR including EGFR mutations and/or EGFR gene amplification, HER2 mutations, or BRAF G466V mutations.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

11.0 LABELING RECOMMENDATIONS

Table 52: Summary of significant labeling changes (FDA table)

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
BOXED WARNING	N/A	In accordance with 21 CFR 201.57 (c)(1), FDA determined QTc prolongation poses a potentially fatal significant risk and created the boxed warning to highlight this risk to health care providers.
INDICATIONS AND USAGE	(b) (4) [redacted]	FDA refined the indication to Include the description "locally advanced or metastatic", selection based upon an FDA-approved test, and to reflect a patient population that had disease progression on or after platinum-based

		chemotherapy.
DOSAGE AND ADMINISTRATION • Dosage Modifications for Adverse Reactions	(b) (4)	Re-ordered the adverse reactions in descending order of seriousness. Revised dosage modification instructions for clarity and brevity, and increased patient safety.
DOSAGE AND ADMINISTRATION • Dosage Modifications for CYP3A Inhibitors (b) (4)	Dosage Modifications for CYP3A Inhibitors (b) (4)	FDA removed instructions for (b) (4)
WARNINGS AND PRECAUTIONS	QTc Prolongation Interstitial Lung Disease Cardiac (b) (4) Diarrhea Embryo-Fetal Toxicity	FDA edited for clarity and brevity, titles were refined to appropriately describe the Adverse Reaction, e.g. QTc Prolongation was changed to QTc Prolongation and Torsades de Pointes, ILD was changed to ILD/pneumonitis, and Cardiac (b) (4) was changed to Cardiac Toxicity. Mitigation strategies were edited in parallel with dosage modification instructions.
ADVERSE REACTIONS		Inclusion of description of pooled population described in Warnings and Precautions section. Edited for accuracy, included per-patient incidence based upon pooled terms to

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		more effectively and comprehensively communicate adverse reaction risks. In addition, the adverse reactions ocular toxicity, abdominal pain, gastroesophageal reflux disease, dyspepsia, decreased weight, pruritus, cough, dyspnea, rhinorrhea, upper respiratory tract infection, musculoskeletal pain, headache, and fatigue were added to the table of common adverse reactions (≥ 10% of patients) based on FDA's review. Clinically significant adverse reactions that occurred at an incidence of < 10% were included in text, namely edema, acute kidney injury, peripheral neuropathy, palmar-plantar erythrodysesthesia, pneumonitis, and cardiac failure. The table describing laboratory abnormalities worsening from baseline was expanded to include all laboratory abnormalities with a cutoff of ≥ 20% of patients.
DRUG INTERACTIONS		Edited for clarity and brevity.
USE IN SPECIFIC POPULATIONS • Females and Males of Reproductive Potential	Recommendation to use effective non-hormonal contraception during treatment with EXKIVITY and for one week following the final dose.	Revised for safety to use contraception during treatment with EXKIVITY and for one month following the final dose.
USE IN SPECIFIC POPULATIONS • Geriatric Use	(b) (4)	Statement that exploratory analysis suggests higher incidence of Grade 3 and 4 adverse reactions in patients

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		over age 65.
(b) (4)		
NONCLINICAL TOXICOLOGY		Inclusion of Section 13.2 Animal Toxicology and/or Pharmacology describing ocular toxicity in dog study.
CLINICAL STUDIES	Description of the primary efficacy population in Study 101 and presentation of ORR and DOR results.	Added demographic details (e.g., number of patients with metastatic disease), clarified details regarding local testing of EGFR exon 20 insertion mutation and modified table with ORR results to only include the ORR as all responses were partial responses.
PATIENT COUNSELING		Re-ordered to highlight importance of counseling for QTc prolongation.

The FDA's Assessment:

The proposed prescribing information has been edited in accordance with 21 Code of Federal Regulations (CFR) and final and draft labeling guidances to ensure the safe and effective use of EXKIVITY.

12.0 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The Applicant's Position:

There is no REMS at this time of submission. This section is not applicable.

The FDA's Assessment:

The risks of mobocertinib are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of mobocertinib can be adequately implemented in the post-marketing setting through product labeling. No additional risk management strategies are recommended.

13.0 POSTMARKETING REQUIREMENTS AND COMMITMENT

The FDA's Assessment:

The following post-marketing requirements and post-marketing commitment will be issued for this application:

PMR #1

Conduct a multicenter, randomized clinical trial and submit the final progression-free survival (PFS) results that verify and describe the clinical benefit of mobocertinib in patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) whose tumors harbor epidermal growth factor receptor (EGFR) exon 20 insertion mutations.

Final Protocol Submission:	01/2021
Trial Completion:	09/2023
Final Report Submission:	03/2024

(b) (4)

PMR #2

Conduct an integrated safety analysis containing data from randomized clinical trials to further characterize the known serious signal of QT prolongation, ventricular arrhythmia and

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Torsades de Pointes. The analyses should include assessment and collection of data to describe the incidence, clinical presentation, management, and outcome of events comprising the Torsades de Pointes SMQ as well as other major adverse cardiovascular events; including arrhythmias, fatal cardiovascular adverse events, and events of sudden death. Detailed narratives of such cases should be included in the final report.

Draft Analysis Plan Submission:	09/2022
Final Analysis Plan Submission:	08/2023
Study Completion:	09/2023
Final Report Submission:	03/2024

(b) (4)

PMR #3

Conduct an integrated safety analysis of data from randomized clinical trials to further characterize the known serious signal of cardiac failure. The analyses should include an assessment of data including left ventricular ejection fraction monitoring to describe the incidence, clinical presentation, management, and outcome of events comprising the cardiac failure and cardiomyopathy standardized MedDRA queries (SMQs) including events of decreased ejection fraction. Detailed narratives of such cases should be included in the final report.

Draft Analysis Plan Submission:	09/2022
Final Analysis Plan Submission:	08/2023
Study Completion:	09/2023
Final Report Submission:	03/2024

(b) (4)

(b) (4)

PMC #1

Conduct an analysis containing data from clinical trials enrolling a sufficient representation of U.S. racial and ethnic minorities including Black/African American patients that is reflective of the US population of patients with EGFR exon 20 insertion mutated NSCLC to further characterize the safety and efficacy of mobocertinib in Black/African American (b) (4) patients with EGFR exon 20 insertion mutated NSCLC.

Draft Analysis Plan Submission:	09/2022
Final Analysis Plan Submission:	08/2023
Study Completion:	09/2023
Final Report Submission:	03/2024

(b) (4)

PMR #4

Conduct a renal impairment clinical trial to evaluate the pharmacokinetics and safety of mobocertinib in patients with normal renal function and patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Draft Guidance for Industry titled: "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing."

Final Protocol Submission:	12/2020
Trial Completion:	09/2022

Final Report Submission: 03/2023

Submit the analysis and datasets with the final report.

PMR #5

Conduct a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of mobocertinib in patients with normal hepatic function and patients with moderate and severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

Final Protocol Submission:	09/2020
Trial Completion:	06/2022
Final Report Submission:	12/2022

Submit the analysis and datasets with final report.

PMR #6

Conduct a study to assess the effect of mobocertinib and its active metabolites on the pharmacokinetics of a breast cancer resistance protein (BCRP) substrate to determine appropriate dosage recommendations when mobocertinib is administered concomitantly with BCRP substrates. Design and conduct the study in accordance with the FDA Guidances for Industry titled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" and "Physiologically Based Pharmacokinetic Analyses — Format and Content"

Draft Analysis Plan Submission:	10/2021
Final Analysis Plan Submission:	12/2021
Study Completion:	04/2022
Final Report Submission:	05/2022

Submit the analysis and datasets with the final report.

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14.0 DIVISION DIRECTOR (OCP)

X _____

Nam Atiqur Rahman, PhD

Reference ID: 4857343

15.0 DIVISION DIRECTOR (OB)

X _____

Shenghui Tang, PhD

Reference ID: 4857343

16.0 DIVISION DIRECTOR (CLINICAL)

I recommend granting accelerated approval to this application for mobocertinib (Exkivity) for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication will be 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 trial(s).

X

Martha Donoghue, MD Deputy Division Director

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17.0 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

Julia Beaver, MD

Chief of Medical Oncology, Oncology Center for Excellence (OCE)

Deputy Office Director (Acting), Office of Oncologic Diseases (OOD)

18.0 APPENDICES

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18.2 Financial Disclosure

The Applicant's Position:

Covered Clinical Study (Name and/or Number):* AP32788-15-101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 622		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 14		
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: _____ Significant payments of other sorts: 14 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study: Applicant of covered study: _____		
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.

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The FDA's Assessment:

A total of 558 investigators participated in Study 101 and provided financial disclosure forms certifying they did not have disclosable financial interests or arrangements. No disclosable financial interests or arrangements for these investigators were reported by the Applicant. Signed financial disclosure forms were not able to be obtained from three sub-investigators; the Applicant made several attempts to obtain the forms without success. However, given that only one patient was enrolled at the sub-investigators' study sites, these missing financial disclosure forms are not likely to impact study integrity.

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18.3 OCP Appendices (Technical Documents Supporting OCP Recommendations)

18.3.1 PPK review summary

Review summary		PopPK modeling was adequate to characterize the PK of mobocertinib and support the label
Goal of PPK analysis		• Characterize the PK of mobocertinib and its active metabolites, AP32960 and AP32914 • Explore the source of mobocertinib PK variability to identify need for individualized dosing • Predict individual exposure for E-R assessment
Study included		AP32788-15-101, TAK-788-1001, TAK-788-1003, TAK-788-1006
Population included		110 healthy subjects and 317 patients
Population characteristics	General	56 yrs (18-86); 69 kg (37.3-132.4); 183 (43%) males;
	Organ impairment	RI: 216 (50.6%) normal, 178 (41.7%) mild, 30 (7%) moderate HI: 369 (86.4%) normal, 54 (12.6%) mild, 1 (0.2%) moderate
Dose(s) included in PPK		5-180 mg QD and 40-60 mg BID
No. of patients, PK samples, and BLQ		427 patients, 16673 PK samples in final PK model; 2.36%, 3.78% and 14.7% of all observations for mobocertinib, AP32960, and AP32914 were below LLOQ, respectively
Model structure		The PK of mobocertinib and AP32960 was described by two-compartment PK models, while a one-compartment model was used to describe the PK of AP32914. Absorption of mobocertinib was described by 3 transit compartments. The observed time-dependent PK was described by an enzyme compartment with drug-dependent stimulation of enzyme production. The enzyme production rate was described by an Emax model based on the molar sum of mobocertinib, AP32960, and AP32914 plasma concentrations, and assumed a similar molar potency of the three moieties. Interindividual variability was estimated on Ka, VcTAK-788/F, CLTAK-788/F, CLAP32960/F, and CLAP32914/F with a full covariance matrix on the clearance and volume terms. Log additive residual error variances were estimated for each of the 3 moieties. The

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	scheme of final popPK model structure was shown in Figure 13.	
Covariates evaluated	Table 18.c	
Model	**Summary**	**Acceptability**
Population characteristics	Table 53, Table 54	
Uncertainty and variability (RSE, IIV, bootstrap)	All of the PK parameters were estimated with good precision (Table 55). The magnitude of the IIV was moderate for CL (49.6% CV) and Vc (48.7% CV). The shrinkage for IIV of CL is also small (<10%).	Yes
BLQ for parameter accuracy	For all moieties the BLQ observations occurring before the Tmax (methodically set at 4 h) were discarded while BLQ values occurring later than 4 hours after dosing were set to LLOQ/2, and subsequent samples below the limit of quantification were discarded.	Yes
GOF, VPC	No signs of model misspecification were identified in the goodness-of-fit plots (Figure 14). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of mobocertinib across different tumor types and dose levels (Figure 15).	Yes
Significant covariates and clinical relevance	Effect of healthy subjects compared to cancer patients on CL and V for 3 moieties were included in the final model. Other evaluated covariates were not included in the model (Figure 16-19).	Yes. None were likely to have clinically meaningful impact on exposure.
Issues with PPK model	**Description**	**Reviewer's analysis**
None		
Labeling language	**Description**	**Acceptability/Action**

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12.3 PK	PK characteristics were based on PPK parameter estimates; specific population information was based on the impact of covariates for PK. No dose adjustment is suggested based on PPK assessment.	Yes

18.3.2 Exposure-Response Analysis

Review summary	**Efficacy**: Based on the exposure from a single dose level (160 mg QD), a positive trend was identified between exposure and best confirmed clinical response in 114 NSCLC patients with EGFR exon 20 insertion mutations (n=114) in Study AP32788-15-101. **Safety**: Based on the exposure ranging from 5 mg to 180 mg QD, positive trends of relationship between exposure and the occurrence of Grade 3+ TEAEs, drug-related Grade 3+ TEAEs, TE SAEs, Grade 3+ diarrhea among 295 patients who received mobocertinib.
Goal of E-R analysis	Evaluate/explore the E-R relationship for efficacy and safety for dose assessment.
E-R for Efficacy	
Study included	**AP32788-15-101** (pivotal)
Exposure variable	Time-averaged exposure (TAE) of molar concentration of the respective compounds (TAK-788, AP32960 and AP32914) (nM.h/day)
Efficacy endpoint	Best confirmed clinical response
No. of patients	114
Dose(s) included	160 mg QD (n=114)
Exposure explored (range)	TAE (710.8, 9788.1 nM.h/day)
Model structure	Graphical quartile analysis, Logistic regression model
Covariates evaluated	Sex, Race, ECOG score, Age, Weight

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Model	Summary	Reviewer's comments
Population characteristics	Table 57	
Visualization of E-R models	Figure 20	Acceptable
Clinical relevance		A positive trend was observed, but result is limited due to small sample size and exposure from a single dose level
E-R for Safety		
Study included	**AP32788-15-101** (pivotal)	
Exposure variable	Time-averaged exposure (TAE) of molar concentration of the respective compounds (TAK-788, AP32960 and AP32914) (nM.h/day)	
Safety endpoint	- Grade 3+ TEAEs - Drug-related Grade 3+ TEAEs - TE SAEs - Grade 3+ diarrhea	
No. of patients	295	
Dose(s) included	5 mg to 180 mg (<160 mg (N=53);160 mg (N=238);180 mg (N=4))	
Exposure explored (range)	TAE (90.1, 10131.6 nM.h/day)	
Model structure	Logistic regression model	
Covariates evaluated	Sex, Race, ECOG score, Age, Weight	
Model	**Summary**	**Reviewer's comments**
Population characteristics	Table 58	
Significant E-R relationship		Positive trends of relationship between time-averaged exposure and the occurrence of Grade 3+ TEAEs, drug-related Grade 3+ TEAEs, TE SAEs, Grade 3+ diarrhea among 295 patients who received mobocertinib. Positive trends of ER relationships for safety endpoints were consistent across different exposure metrics (total sum of molar concentration, parent molar

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		concentration or metabolite molar concentration).
Visualization of E-R models	Figure 21, Figure 22	Acceptable
Clinical relevance		The positive ER trend for safety supports the dose reduction due to AE
Issues with E-R analysis	**Description**	**Reviewer's analysis**
None		
Labeling language	**Description**	**Acceptability/Action**
12.2 Pharmacodynamics	A required section according to 21 CFR 201.57(c)(13)(i)(B).	A generic statement was added given an inconclusive E-R analysis from a single dose study.

Table 53: Descriptive Statistics of Continuous Baseline Demographic Characteristics, Laboratory, and Disease Status Variables of the Subjects included in the Analysis Dataset

	AP32788-15-101 part 1 & 2	AP32788-15-101 part 3	TAK-788-1001	TAK-788-1003	TAK-788-1006	Overall
Individuals						
N	201	96	86	20	24	427
Age (years)						
Mean (SD)	61.3 (11.0)	59.1 (11.7)	28.7 (9.77)	59.8 (11.1)	39.0 (8.45)	52.9 (17.0)
Median (IQR)	62.0 (54.0-69.0)	59.0 (52.0-68.0)	25.0 (21.3-32.0)	61.0 (53.0-67.3)	40.5 (33.0-44.3)	56.0 (43.0-66.0)
Min-max	24.0-86.0	27.0-80.0	18.0-54.0	41.0-83.0	25.0-55.0	18.0-86.0
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bodyweight (kg)						
Mean (SD)	70.2 (16.9)	65.3 (15.0)	76.9 (10.7)	54.7 (9.77)	82.9 (11.1)	70.4 (15.9)
Median (IQR)	67.3 (57.8-80.0)	63.5 (55.7-74.1)	78.0 (70.0-86.5)	52.8 (48.3-60.8)	81.8 (72.8-92.3)	69.0 (58.8-81.6)
Min-max	41.7-132	37.3-112	47.1-94.9	39.1-74.1	64.9-100	37.3-132
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Albumin (g/L)						
Mean (SD)	37.9 (5.66)	44.2 (42.1)	45.2 (3.22)	37.8 (4.81)	45.4 (1.89)	41.2 (20.7)
Median (IQR)	39.0 (35.0-42.0)	40.0 (37.0-43.9)	45.0 (44.0-47.0)	38.0 (36.5-40.3)	45.5 (44.8-46.0)	41.0 (37.0-44.0)
Min-max	3.50-50.0	28.0-450	36.0-52.0	25.0-46.0	42.0-50.0	3.50-450
Missing	1 (0.498%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.234%)
Aspartate transaminase (AST) (U/L)						
Mean (SD)	25.9 (14.3)	25.4 (15.0)	18.1 (4.50)	23.8 (9.20)	19.6 (7.17)	23.7 (12.9)
Median (IQR)	22.0 (18.0-29.0)	23.5 (18.0-28.6)	17.0 (15.0-20.0)	24.0 (17.8-29.3)	17.0 (15.8-21.0)	21.0 (16.0-27.0)
Min-max	9.00-106	9.00-145	10.0-34.0	10.0-39.0	13.0-47.0	9.00-145
Missing	1 (0.498%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.234%)
Alanine transaminase (ALT) (U/L)						
Mean (SD)	24.5 (20.8)	20.9 (10.3)	18.0 (6.56)	17.2 (11.7)	20.3 (8.68)	21.8 (15.9)

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	AP32788-15-101 part 1 & 2	AP32788-15-101 part 3	TAK-788-1001	TAK-788-1003	TAK-788-1006	Overall
Median (IQR)	20.0 (14.0-26.3)	19.0 (13.8-26.0)	17.0 (13.0-22.8)	14.0 (11.0-19.8)	18.0 (15.0-23.5)	18.0 (14.0-24.8)
Min-max	4.00-186	6.00-67.0	7.00-38.0	5.00-55.0	9.00-42.0	4.00-186
Missing	1 (0.498%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.234%)
Bilirubin (µmol/L)						
Mean (SD)	7.97 (4.18)	10.2 (4.18)	12.1 (4.38)	11.4 (6.80)	8.84 (4.77)	9.50 (4.68)
Median (IQR)	7.00 (5.00-9.00)	10.2 (7.34-12.0)	12.0 (8.55-13.7)	8.55 (6.84-12.4)	6.84 (6.84-8.98)	9.00 (6.84-12.0)
Min-max	0.400-27.0	3.42-26.0	5.13-25.7	5.13-34.2	5.13-25.7	0.400-34.2
Missing	1 (0.498%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.234%)
Creatinine Clearance (mL/min)						
Mean (SD)	85.3 (30.6)	89.1 (27.3)	120 (18.6)	77.7 (20.9)	127 (21.0)	95.3 (31.2)
Median (IQR)	81.6 (65.3-100)	89.0 (70.7-106)	119 (108-132)	72.8 (66.7-93.9)	125 (111-137)	93.7 (72.6-113)
Min-max	26.3-251	43.0-204	86.6-168	38.3-113	95.2-186	26.3-251
Missing	3 (1.49%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.703%)
Estimated Glomerular Filtration rate as per MDRD equation (ml/min/1.73m²)						
Mean (SD)	87.5 (29.4)	98.3 (29.6)	96.1 (14.9)	102 (25.7)	94.1 (15.7)	92.7 (26.7)
Median (IQR)	84.6 (67.7-103)	93.9 (82.8-115)	95.5 (85.7-106)	99.6 (87.7-119)	96.3 (82.3-103)	90.6 (76.2-107)
Min-max	33.6-304	46.1-231	66.4-147	53.2-147	68.2-122	33.6-304
Missing	3 (1.49%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.703%)

Source: Applicant's PopPK report, Table 16, Page 101

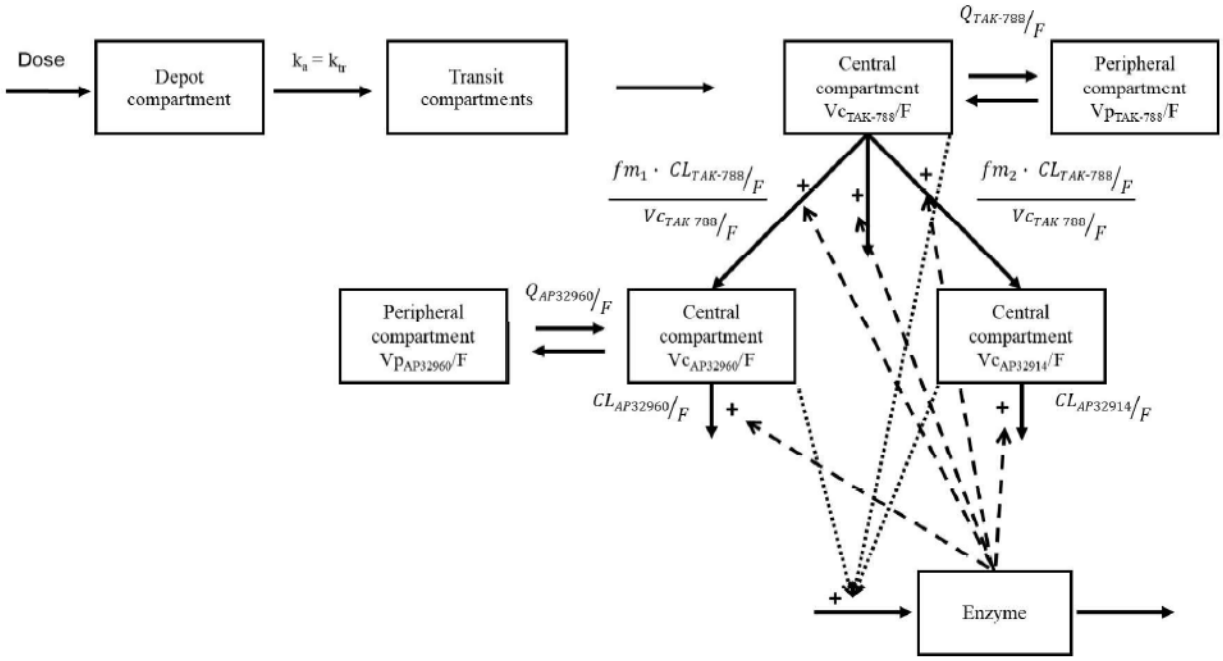
Table 54: Descriptive Statistics of Categorical Baseline Demographic Characteristics, Laboratory, and Disease Status Variables of the Subjects included in the Analysis Dataset

	AP32788-15-101 part 1 & 2	AP32788-15-101 part 3	TAK-788-1001	TAK-788-1003	TAK-788-1006	Overall
Individuals						
N	201	96	86	20	24	427
Sex						
Male	66 (32.8%)	34 (35.4%)	65 (75.6%)	6 (30.0%)	12 (50.0%)	183 (42.9%)
Female	135 (67.2%)	62 (64.6%)	21 (24.4%)	14 (70.0%)	12 (50.0%)	244 (57.1%)
Race						
White	151 (75.1%)	28 (29.2%)	82 (95.3%)		22 (91.7%)	283 (66.3%)
Black	13 (6.47%)	2 (2.08%)	4 (4.65%)			19 (4.45%)
Asian	29 (14.4%)	66 (68.8%)		20 (100%)		115 (26.9%)
American Indian/Alaskan Native					1 (4.17%)	1 (0.234%)
Other / Multiple	8 (3.98%)				1 (4.17%)	9 (2.11%)
Mutation status						
EGFR / HER mutant	4 (1.99%)					4 (0.937%)
EGFR mutant	162 (80.6%)			19 (95.0%)		181 (42.4%)
HER mutant	35 (17.4%)			1 (5.00%)		36 (8.43%)
Other		96 (100%)	86 (100%)		24 (100%)	206 (48.2%)
Smoking status						
Never	129 (64.2%)	70 (72.9%)	86 (100%)	12 (60.0%)	23 (95.8%)	320 (74.9%)
Former	70 (34.8%)	24 (25.0%)		8 (40.0%)	1 (4.17%)	103 (24.1%)
Current	1 (0.498%)	2 (2.08%)				3 (0.703%)
Unknown	1 (0.498%)					1 (0.234%)
Patient status						
Patient	201 (100%)	96 (100%)		20 (100%)		317 (74.2%)
Healthy Volunteer			86 (100%)		24 (100%)	110 (25.8%)
	AP32788-15-101 part 1 & 2	**AP32788-15-101 part 3**	**TAK-788-1001**	**TAK-788-1003**	**TAK-788-1006**	**Overall**
Formulation						
Capsule A/B	201 (100%)		86 (100%)		12 (50.0%)	299 (70.0%)
Capsule C		96 (100%)		20 (100%)	12 (50.0%)	128 (30.0%)
Prior Treatment						
TAK-788 First line	28 (13.9%)					28 (6.56%)
TAK-788 Second line or later	173 (86.1%)	96 (100%)		20 (100%)		289 (67.7%)
Healthy Volunteer			86 (100%)		24 (100%)	110 (25.8%)

Source: Applicant's PopPK report, Table 17, Page 103

Reference ID: 4857343

Figure 13: Structure of Final PopPK model



Source: Applicant's PopPK report, Page 6

Table 55: Subject-specific baseline covariates examined in the population PK analysis

Parameter	Baseline covariates
Absorption parameters	• *Demographics:* race, sex • *Disease related:* cancer patient/healthy subject • *Drug related:* formulation
Apparent oral clearance parameters	• *Demographics:* age, body weight (BW), race, sex, smoking status • *Laboratory values:* albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine clearance (CrCL), estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) formula • *Disease related:* cancer patient/healthy subject
Apparent volume of distribution parameters	• *Demographics:* age, BW, race, sex • *Laboratory values:* albumin • *Disease related:* cancer patient/healthy subject

Source: Applicant's PopPK report, Table 2, Page 6

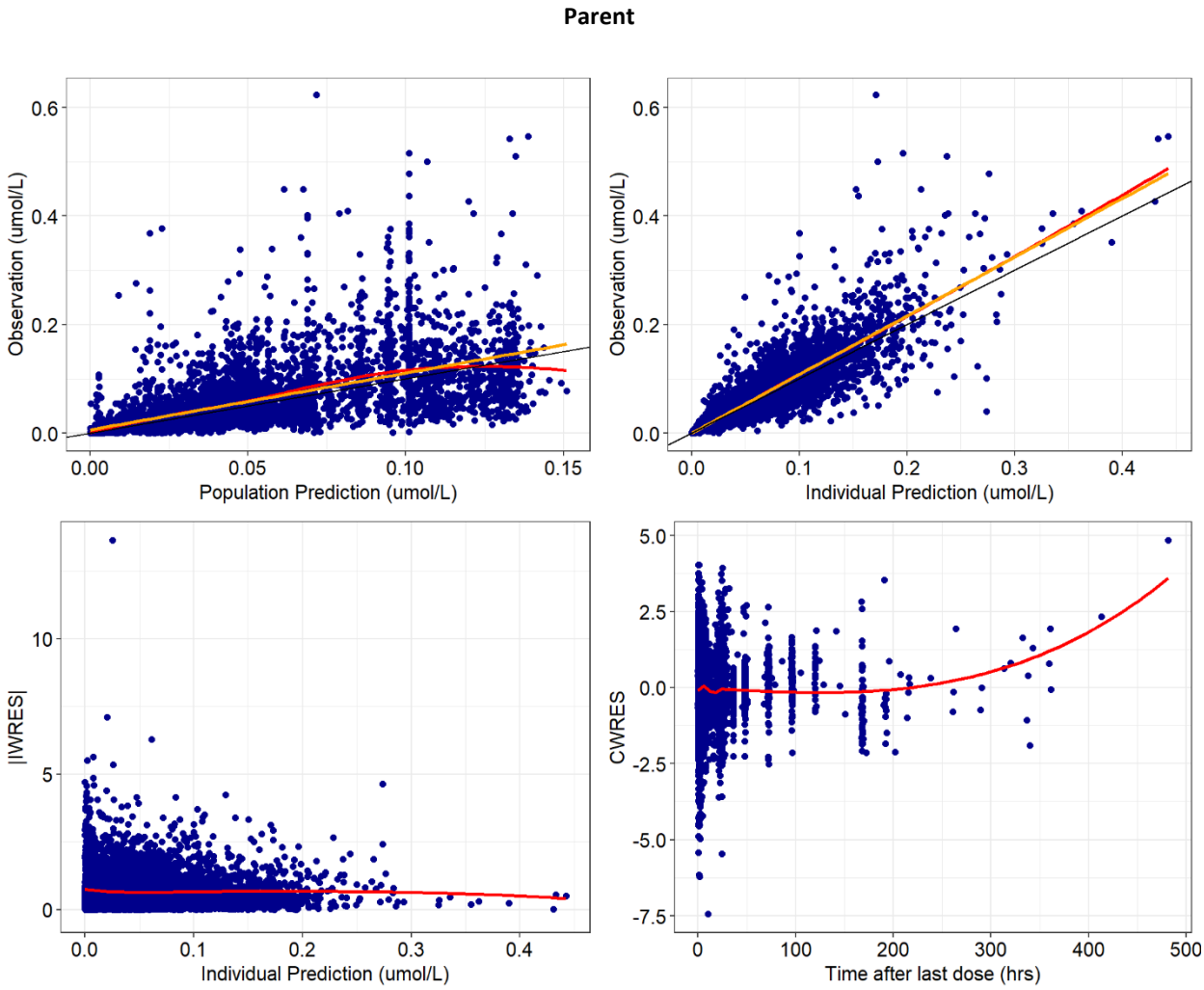
Table 56: Parameter Estimates of the Base and Final PopPK Model

Parameter	Estimate	RSE (%)	Bootstrap 95%CI	Shrinkage (%)	Untransformed parameter
Population Parameter					
Ka	0.752	3.29	[2.02 ; 2.23]	-	2.12 h^{-1}
$Vc_{TAK-788}/F$	7.76	0.418	[2200 ; 2500]	-	2340 L
$CL_{TAK-788}/F$	4.68	0.928	[95.2 ; 116]	-	108 L/h
$Q_{TAK-788}/F$	2.46	12.6	[6.59 ; 25.4]	-	11.7 L/h
$Vp_{TAK-788}/F$	7.01	1.68	[888 ; 1440]	-	1110 L
$CL_{AP32960}/F$	4.76	0.834	[103 ; 124]	-	117 L/h
$Vc_{AP32960}/F$	2.55	4.23	[9.94 ; 15.1]	-	12.8 L
$Q_{AP32960}/F$	3.28	1.31	[23.7 ; 28.4]	-	26.5 L/h
$Vp_{AP32960}/F$	6.99	1.12	[914 ; 1240]	-	1090 L
$CL_{AP32914}/F$	4.82	0.901	[109 ; 134]	-	124 L/h
$Vc_{AP32914}/F$	3.42	2.06	[25.7 ; 34.2]	-	30.6 L
HV on $Vc_{TAK-788}/F$	0.787	12.7	[0.591 ; 0.987]	-	0.787
HV on $CL_{TAK-788}/F$	0.900	15.0	[0.680 ; 1.28]	-	0.900
HV on $CL_{AP32960}/F$	0.738	13.0	[0.581 ; 1.00]	-	0.738
HV on $CL_{AP32914}/F$	0.909	15.0	[0.676 ; 1.27]	-	0.909
K_{enz}	-5.54	3.26	[0.00272 ; 0.00673]	-	0.00392 h^{-1}
EC_{50}	-1.55	39.6	[16.9 ; 225000]	-	213 nM
E_{MAX}	0.781	44.9	[0.301 ; 417]	-	0.781
Interindividual Variability					
ETA Ka	0.209	10.5	[41.6 ; 50.7]	3.43	45.7 %
ETA $Vc_{TAK-788}/F$	0.237	9.97	[44.0 ; 53.6]	6.88	48.7 %
ETA $CL_{TAK-788}/F$	0.246	8.36	[45.2 ; 53.8]	2.92	49.6 %
Cov ETA $CL_{TAK-788}/F$- ETA $Vc_{TAK-788}/F$	0.197	9.12	[0.161 ; 0.235]	-	0.814
ETA $CL_{AP32960}/F$	0.157	9.85	[35.7 ; 43.8]	3.69	39.6 %
Cov ETA $CL_{AP32960}/F$- ETA $Vc_{TAK-788}/F$	0.153	9.62	[0.125 ; 0.188]	-	0.794
Cov ETA $CL_{AP32960}/F$- ETA $CL_{TAK-788}/F$	0.182	9.35	[0.149 ; 0.220]	-	0.927
ETA $CL_{AP32914}/F$	0.295	7.93	[49.7 ; 58.5]	3.23	54.3 %
Cov ETA $CL_{AP32960}/F$- ETA $Vc_{TAK-788}/F$	0.194	9.98	[0.157 ; 0.235]	-	0.735
Cov ETA $CL_{AP32914}/F$- ETA $CL_{TAK-788}/F$	0.221	8.79	[0.181 ; 0.262]	-	0.821
Cov ETA $CL_{AP32914}/F$- ETA $CL_{AP32960}/F$	0.171	9.85	[0.138 ; 0.210]	-	0.797
Residual Variability					
Additive error on log scale TAK-788	0.414	3.20	[0.389 ; 0.441]	5.07	41.4 %
Additive error on log scale AP32960	0.373	4.28	[0.344 ; 0.405]	5.03	37.3 %
Additive error on log scale AP32914	0.405	3.23	[0.379 ; 0.431]	5.55	40.5 %

Reference ID: 4857343

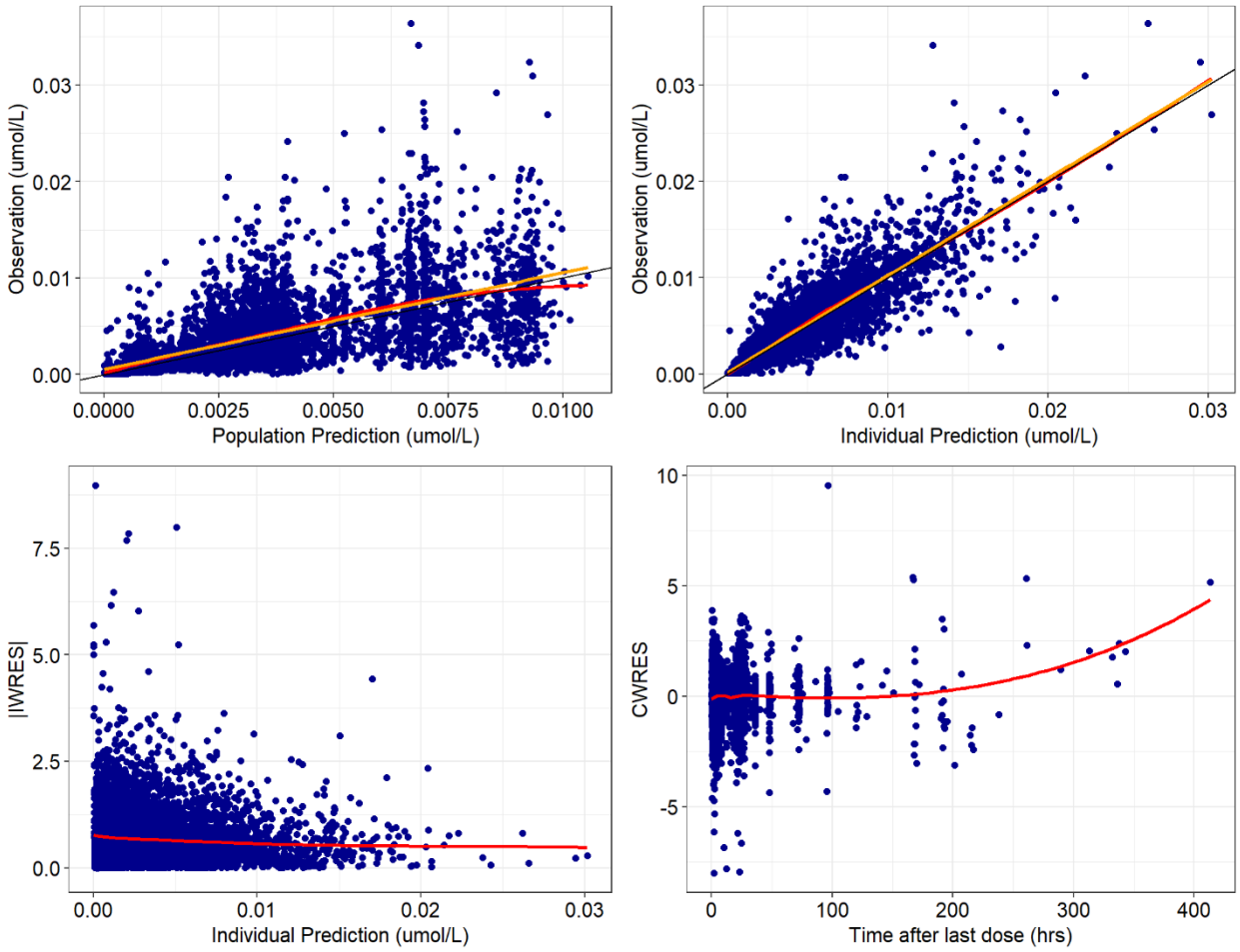
Source: Applicant's PopPK report, Table 11, Page 48

Figure 14: Goodness of Fit Plots of the Final Model



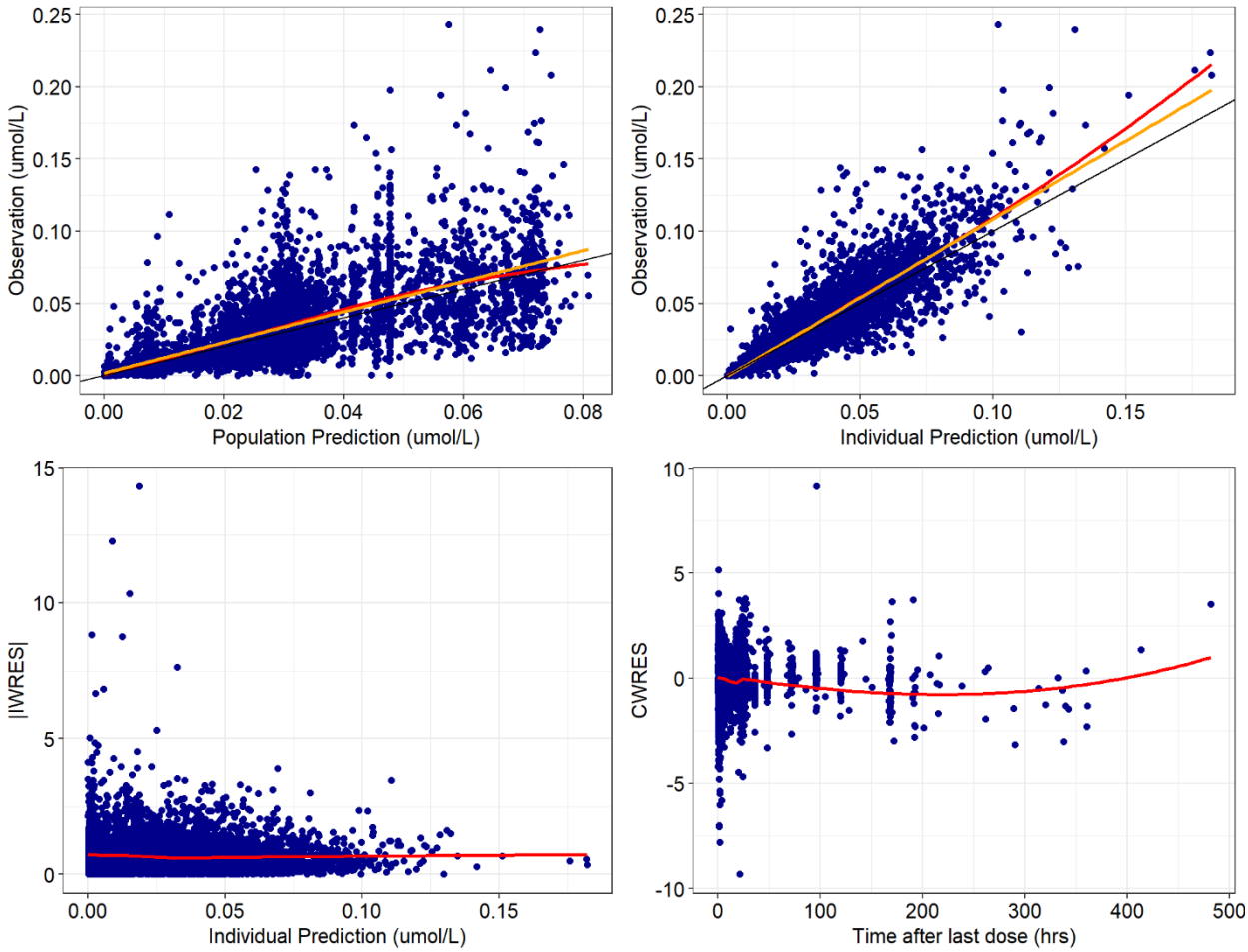
Reference ID: 4857343

AP32914



Reference ID: 4857343

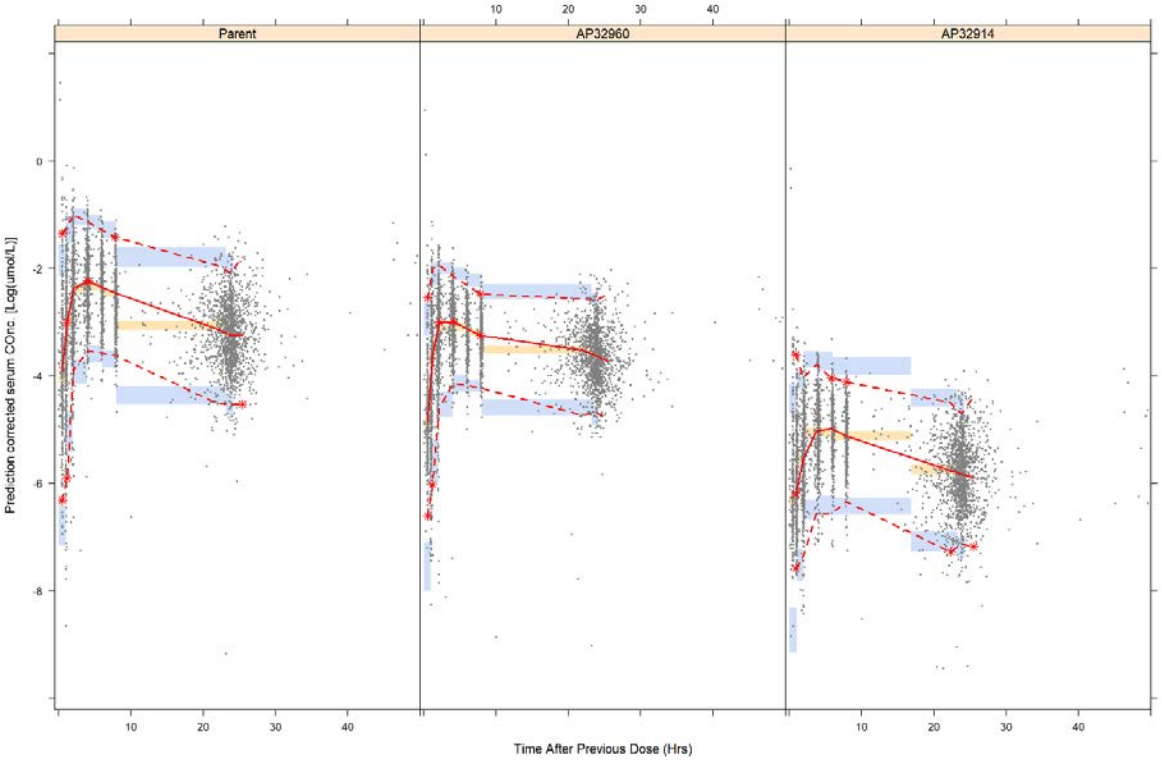
AP32960



Source: Reviewer's Analysis based on dataset "poppk.xpt"

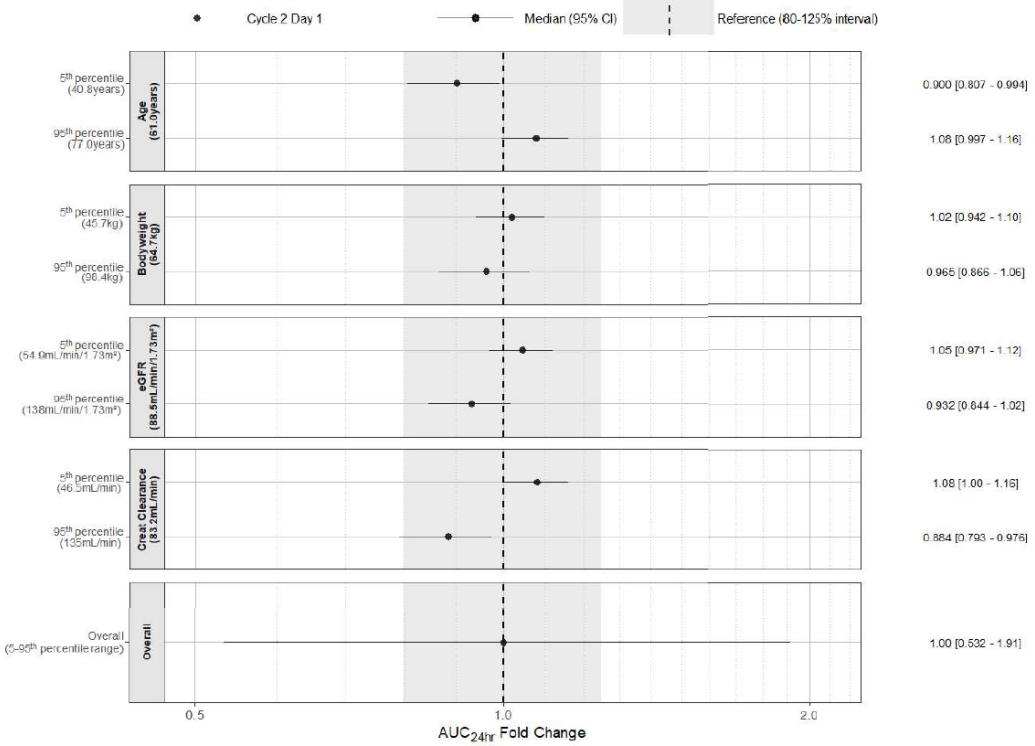
Reference ID: 4857343

Figure 15: Visual Predictive Checks Concentration-Time Profiles for Mobocertinib and Its Two Active Metabolites AP32960 and AP32914.

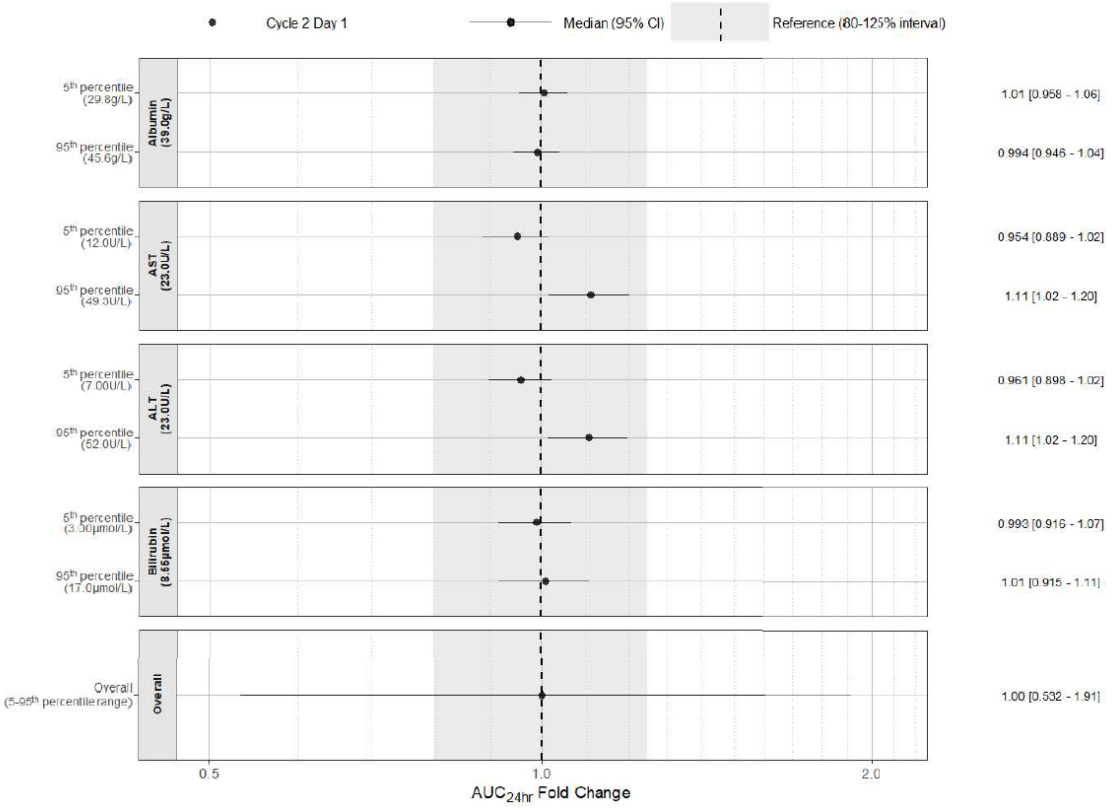


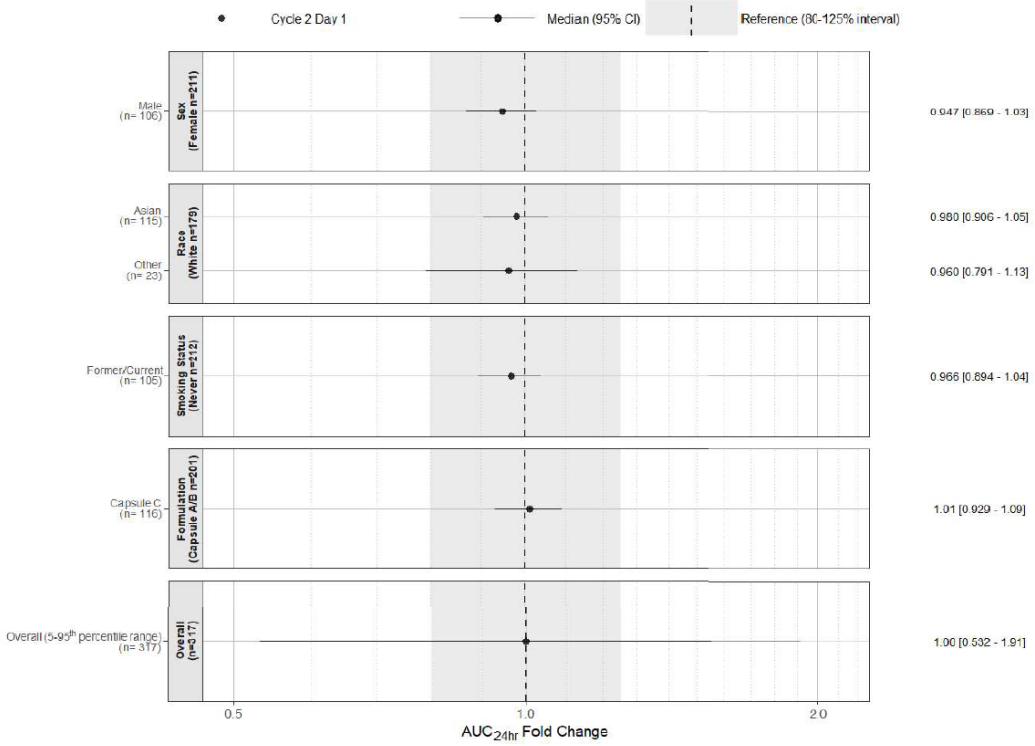
Source: Reviewer's Analysis based on dataset "poppk.xpt"

Figure 16: Covariate Effects on Molar Sum Exposure Following 160 mg QD Doses at Cycle 2 Day 1.



Reference ID: 4857343

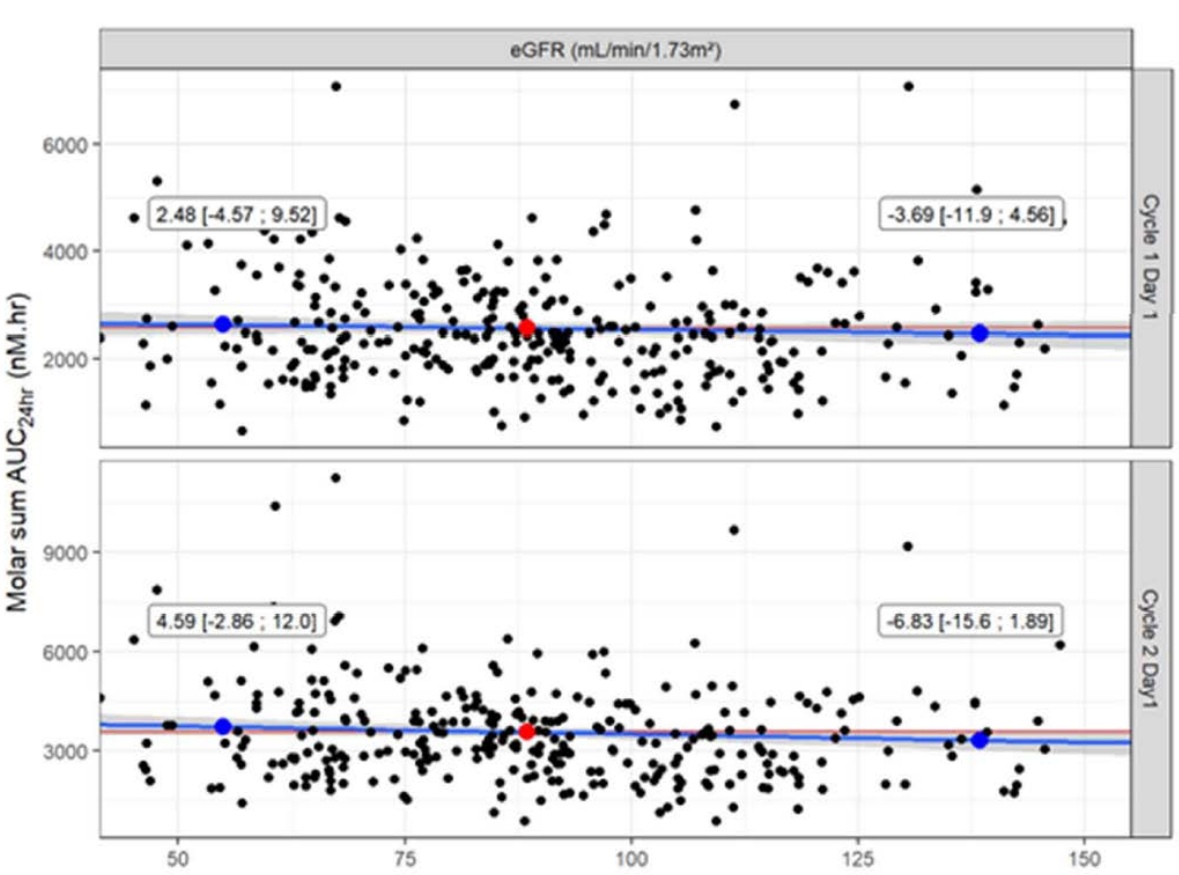

Cycle 2 Day 1
Median (95% CI)
Reference (80-125% interval)
5th percentile (29.8g/L)
95th percentile (45.6g/L)
Albumin (39.0g/L)
1.01 [0.958 - 1.06]
0.994 [0.946 - 1.04]
5th percentile (12.0U/L)
95th percentile (49.3U/L)
AST (23.0U/L)
0.954 [0.889 - 1.02]
1.11 [1.02 - 1.20]
5th percentile (7.00U/L)
95th percentile (52.0U/L)
ALT (23.0U/L)
0.961 [0.898 - 1.02]
1.11 [1.02 - 1.20]
5th percentile (3.00µmol/L)
95th percentile (17.0µmol/L)
Bilirubin (8.55µmol/L)
0.993 [0.916 - 1.07]
1.01 [0.915 - 1.11]
Overall (5-95th percentile range)
Overall
1.00 [0.532 - 1.91]
0.5
1.0
2.0
AUC24hr Fold Change



Source: Applicant's PopPK report, Figure 13-14, Page 59

The magnitudes of percent difference in combined molar AUC24 at the 5th or 95th percentiles of CrCL or eGFR relative to the median combined molar AUC24 were <15% on both Cycle 1 Day 1 and Cycle 2 Day 1. Similarly, the magnitudes of percent difference in combined molar AUC24 at the 5th or 95th percentiles of bilirubin, ALT, or AST relative to the median combined molar AUC24 were <15% on both Cycle 1 Day 1 and Cycle 2 Day 1, suggesting the lack of a clinically meaningful effect of bilirubin, ALT, or AST on mobocertinib PK. This suggests that no dose adjustment is necessary for patients with mild hepatic impairment, or patients with mild or moderate renal impairment.

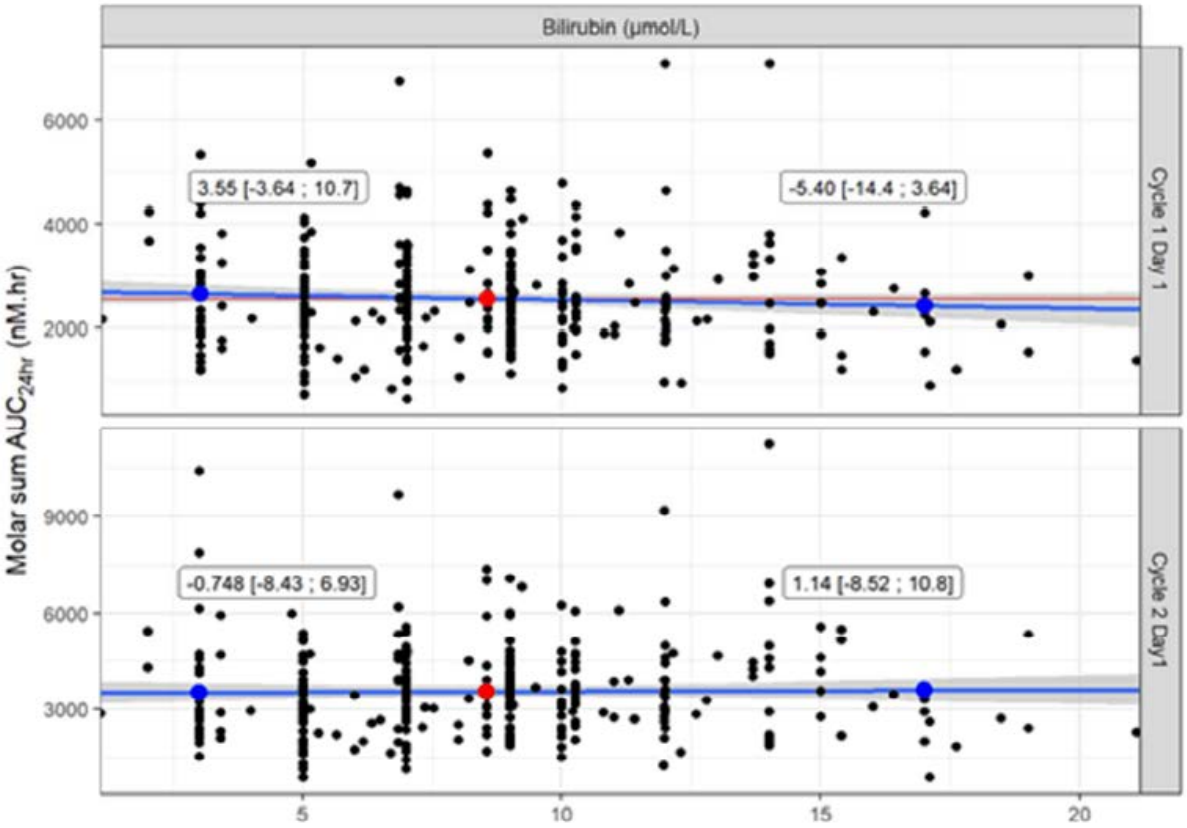
Figure 17: Individual Predicted Combined Molar AUC24 of Mobocertinib, AP32960, and AP32914 Versus Estimated Glomerular Filtration Rate for Patients with NSCLC.



Source: Applicant's Clinical Pharmacology Summary, Figure 3.g, Page 109

Reference ID: 4857343

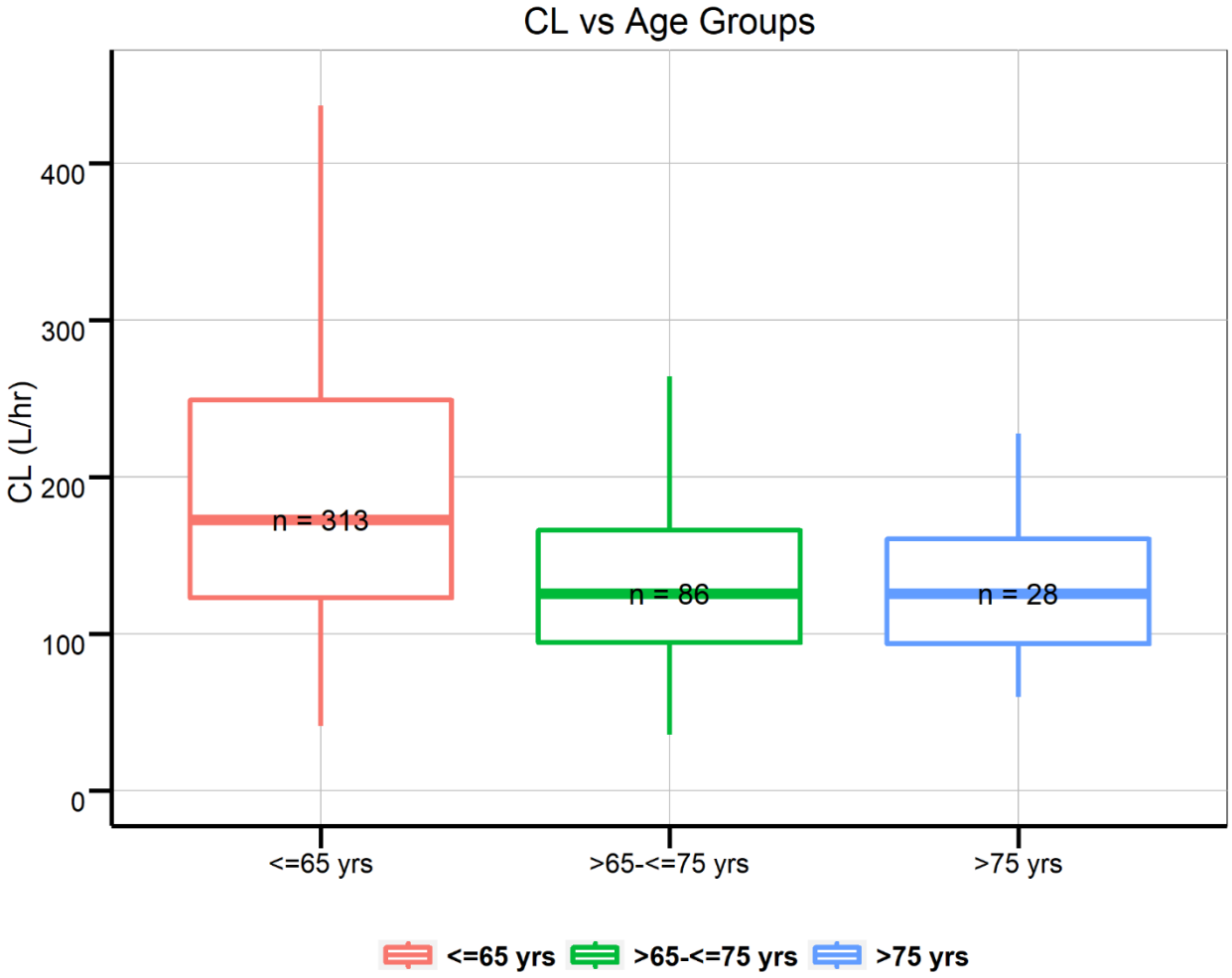
Figure 18: Individual Predicted Combined Molar AUC24 of Mobocertinib, AP32960, and AP32914 Versus Bilirubin in Patients with NSCLC.



Source: Applicant's Clinical Pharmacology Summary, Figure 3.h, Page 111

Reference ID: 4857343

Figure 19: Individual Predicted Clearance of Mobocertinib at Steady State Versus Patients in Different Age Groups.



Source: Reviewer's analysis based on Table 24 in Applicant's popPK report

Reference ID: 4857343

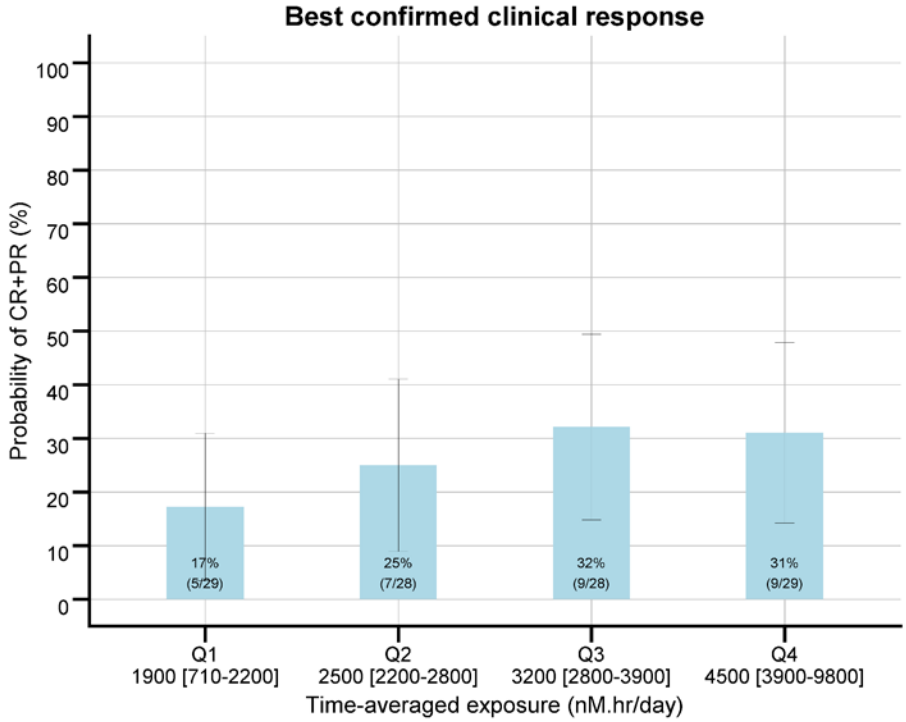
Table 57: Demographic Characteristics by Exposure Quartiles in the ER Efficacy Analysis Dataset

Covariate	value	Q1 1900 [710-2200]	Q2 2500 [2200-2800]	Q3 3200 [2800-3900]	Q4 4500 [3900-9800]
Number of Subjects		29	28	28	29
Age		61 (12.6)	56.5 (10.5)	63 (9.9)	64 (12.4)
Body Weight		64 (13.1)	64.4 (12.8)	65.7 (15.8)	67.5 (16)
Baseline ECOG	0	9 (31%)	7 (25%)	7 (25%)	7 (24.1%)
Baseline ECOG	1	20 (69%)	21 (75%)	21 (75%)	22 (75.9%)
Race	White	15 (51.7%)	7 (25%)	10 (35.7%)	10 (34.5%)
Race	Black	1 (3.4%)	1 (3.6%)	1 (3.6%)	NA
Race	Asian	13 (44.8%)	19 (67.9%)	17 (60.7%)	19 (65.5%)
Race	Other	NA	1 (3.6%)	NA	NA
Gender	Male	8 (27.6%)	14 (50%)	10 (35.7%)	7 (24.1%)
Gender	Female	21 (72.4%)	14 (50%)	18 (64.3%)	22 (75.9%)

Source: Reviewer's Analysis based on dataset "er.xpt"

Reference ID: 4857343

Figure 20: Relationship between Mobocertinib Exposure and BCR in Patients with NSCLC.



Source: Reviewer's Analysis based on dataset "er.xpt"

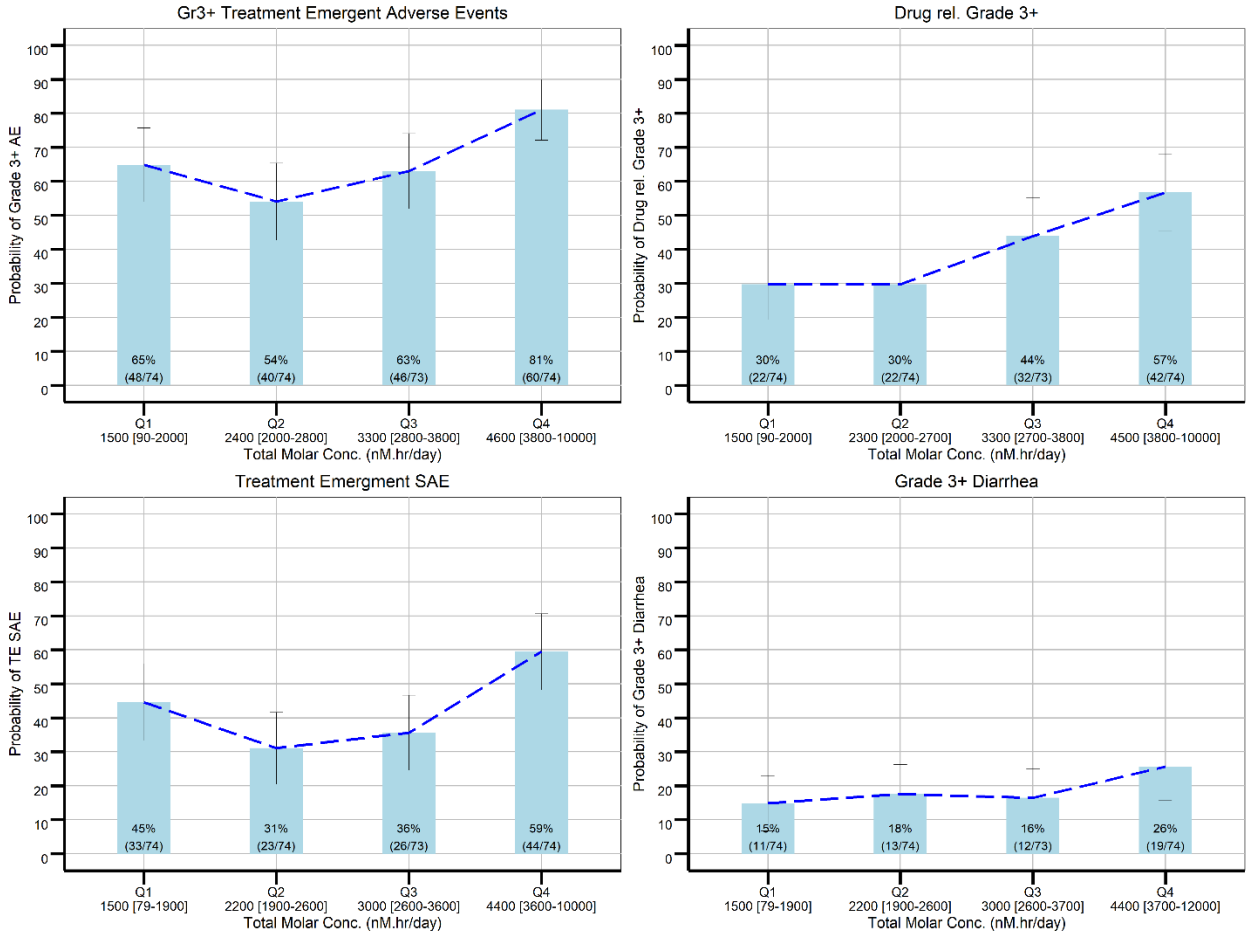
Table 58: Demographic Characteristics by Exposure Quartiles in the ER Safety Analysis Dataset

Covariate	value	Q1 1500 [90-2000]	Q2 2400 [2000-2800]	Q3 3300 [2800-3800]	Q4 4600 [3800-10000]
Number of Subjects		74	74	73	74
Age		59 (11.2)	59.5 (11.9)	61 (9.1)	65 (12.5)
Body Weight		64.8 (16.1)	64.2 (15.2)	67.5 (17.4)	65.6 (17.2)
Baseline ECOG	0	20 (27%)	26 (35.1%)	22 (30.1%)	19 (25.7%)
Baseline ECOG	1	54 (73%)	48 (64.9%)	51 (69.9%)	55 (74.3%)

Race	White	49 (66.2%)	42 (56.8%)	41 (56.2%)	45 (60.8%)
Race	Black	5 (6.8%)	4 (5.4%)	2 (2.7%)	4 (5.4%)
Race	Asian	18 (24.3%)	27 (36.5%)	26 (35.6%)	24 (32.4%)
Race	Other	2 (2.7%)	1 (1.4%)	4 (5.5%)	1 (1.4%)
Gender	Male	22 (29.7%)	28 (37.8%)	29 (39.7%)	21 (28.4%)
Gender	Female	52 (70.3%)	46 (62.2%)	44 (60.3%)	53 (71.6%)

Source: Reviewer's Analysis based on dataset "er.xpt"

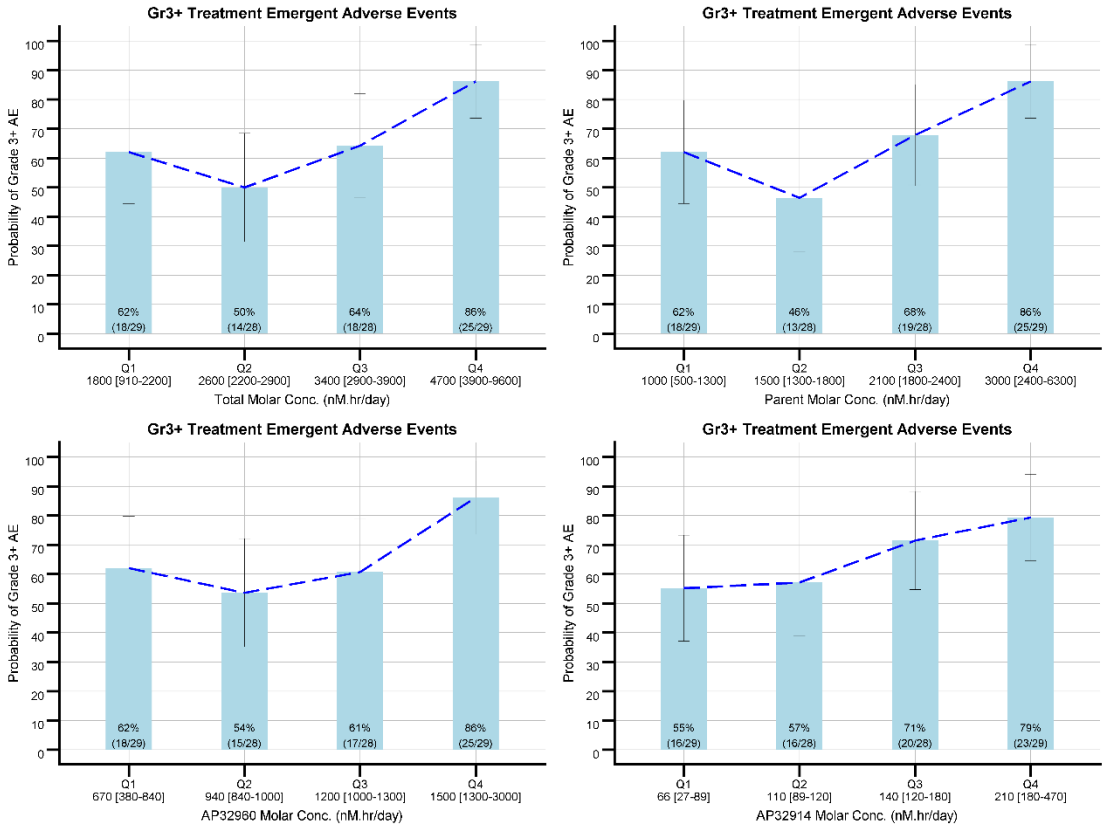
Figure 21: Relationship between Mobocertinib Exposure and Evaluated Safety Endpoints in Patients with NSCLC.



Source: Reviewer's Analysis based on dataset "er.xpt"

Reference ID: 4857343

Figure 22: Relationship between Mobocertinib Exposure and Gr3+ TEAE across Different Exposure Metrics in Patients with NSCLC.



Source: Reviewer's Analysis based on dataset "er.xpt"

18.3.3 Physiologically based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate the drug-drug interaction (DDI) for mobocertinib, and its two active metabolites, AP32960 and AP32914, as CYP3A substrates and perpetrators. The Division of Pharmacometrics has reviewed the PBPK report, supporting modeling files, the applicant's responses to Clinical Pharmacology Information Requests (IRs) and concluded the following.

- The PBPK analysis is adequate to evaluate the effects of CYP3A inhibitors on the PK of mobocertinib. The model predicted that a strong CYP3A inhibitor (such as itraconazole and ketoconazole) may increase the steady state combined molar exposure of mobocertinib, AP32960, and AP32914 by approximately 400%; a moderate CYP3A inhibitor may increase the combined molar exposure by approximately 120%-230%.

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- The PBPK analysis is adequate to evaluate the effects of CYP3A inducers on the PK of mobocertinib. The model predicted that a strong CYP3A inducer, rifampin, may decrease the steady state combined molar exposure of mobocertinib, AP32960, and AP32914 by more than 90%; a moderate CYP3A inducer, efavirenz, may decrease the combined molar exposure by approximately 60%.
- The effect of mobocertinib on the PK of a CYP2C8 substrate is minimal.
- The PBPK analysis is adequate to evaluate the effect of mobocertinib on the PK of a P-gp substrate. The effect of mobocertinib on a P-gp substrate is predicted to be low.
- The PBPK analysis is inadequate to evaluate the effect of mobocertinib on the PK of a BCRP substrate because whether the sulfasalazine (a BCRP substrate) model can detect a positive DDI is unknown, and the in vitro to in vivo extrapolation on the Ki has not been established for the BCRP-mediated DDIs.

Background

TAK-788 (mobocertinib; AP32788) is being developed for the treatment of patients with NSCLC (non-small cell lung cancer). TAK-788 has 2 active metabolites, AP32960 and AP32914, which have similar activity to TAK-788 in kinase and cellular assays.

Mobocertinib exhibits high solubility in pH range of 1 to 6.8, and high permeability. The absolute bioavailability (BA) of mobocertinib is 37% based on mass balance (Study TAK-788-1002). Food has no impact on the PK of mobocertinib.

In vitro, mobocertinib, AP32960 and AP32914 are mainly metabolized by CYP3A4. In vitro, mobocertinib, AP32960, and AP32914 were P-gp substrates in at least one test system (Caco-2 cells and MDR1-overexpressing MDCK cells) and AP32960 was a BCRP substrate in BCRP-overexpressing MDCK cells. P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of mobocertinib clinically because mobocertinib exhibits high solubility and high permeability in vitro.

In vitro, mobocertinib, AP32960 and AP32914 showed mechanism-based inhibition and induction towards CYP3A4, competitive inhibition towards CYP3A4, CYP2B6, CYP2C8, CYP2C9, and inhibition towards P-gp and BCRP. Based on the static model, mobocertinib is not expected to inhibit CYP2B6, and CYP2C9 in vivo. In human hepatocytes, AP32914 at >= 1 μM induced the mRNA expression of CYP1A2 by 3.4- to 5.6-fold, and mobocertinib at >= 1 μM induced the mRNA expression of CYP2B6 by approximately 3.0-fold. Based on the correlation method, the in vivo induction potential towards CYP1A2 or CYP2B6 is low. Therefore, the PBPK analyses assessing the effect of mobocertinib (and its metabolites) on the PK of CYP2B6 (bupropion and OH-bupropion), or CYP2C9 (S-warfarin) substrates are not evaluated.

Clinical DDI studies were conducted with itraconazole and rifampin (TAK-788-1006), as well as midazolam (TAK-788-1004).

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The applicant submitted two PBPK analyses reports: "Development of a PBPK model for TAK-788 and its active metabolites (AP32960 and AP32914) within the Simcyp population-based simulator and subsequent evaluation of DDI liability (pbpk-rpt-tak-788)" and "Development of a Physiologically Based Absorption and Pharmacokinetic (PBPK) Model for TAK-788 Using GastroPlus® (report No. 019120J)".

Three formulations have been developed (DiC-A, DiC-B, and DiC-C (size 1 and size 2)). DiC-A and DiC-B have been demonstrated to be bioequivalent (TAK-788-1001 part 3). DiC-C (size 1) was used in the pivotal clinical trial (AP32788-15-101 part 3), and DiC-C (size 2) is the to-be-marketed formulation. The formulations used in the relevant studies are summarized in Table 59. The aim of the report '019120J' was to demonstrate the bioequivalence (BE) between DiC-C (size 1) and DiC-B, and DiC-C (size 1) and DiC-C (size 2). In the 'pbpk-rpt-tak-788' report, the same absorption model and parameters were used across different studies and formulations (Table 59). As the model appears to be able to describe the PK and given that mobocertinib is a highly soluble and highly permeable drug, the formulation difference is not expected to have significant effect on the DDI evaluation. This review focuses on evaluating the DDI potentials for mobocertinib.

Methods

Model development and validation

PBPK models were developed for TAK-788 (mobocertinib), AP32960 and AP32914 in Simcyp (Certara Version 18). The studies used for model calibration and validation are summarized in Table 56 Briefly, the total clearance of mobocertinib was obtained from the absolution bioavailability (BA) / mass balance study. The fractions metabolized by CYP3A3 (fmCYP3A4) for mobocertinib, AP32914, and AP32960 were derived from the itraconazole DDI study. The CYP3A time-dependent inhibition (TDI) parameters for mobocertinib, AP32960 and AP32914 were obtained from the in vitro study. The CYP3A induction parameters were obtained from the midazolam DDI study and multiple dose PK study following 160 mg QD administration.

Table 59: Summary of studies used for model development and validation (report pbpk-rpt-tak-788)

Modeling stage	Study	Brief description	Formulation	Population	Parameters obtained
Development	TAK-788-1002	Absolute BA / mass balance	DiC-C	HVs	CL for TAK-788
	TKD-BCS-00600-R1	Metabolite identification study		HVs	Fa for TAK-788, fm AP32960 formation
	TAK-788-1006	Itraconazole DDI	DiC-A (BE to DiC-B)	HVs	fmCYP3A4 for TAK-788, AP32914, and AP32960
	AP32788-15-101	SAD / MAD (160 mg)	DiC-A / DiC-B / DiC-C	NSCLC	CYP3A4 induction, and fumic

	TAK-788-1004	Midazolam DDI	DiC-C	NSCLC	CYP3A4 Indmax
Validation	AP32788-15-101	SAD / MAD	DiC-A / DiC-B / DiC-C	NSCLC	Dose linearity, CYP3A4 induction, TDI, and non-specific binding
	TAK-788-1006	Rifampin DDI	DiC-C	HVs	Verification of fmCYP3A4 for TAK-788, AP32914, and AP32960
	TAK-788-1004	Midazolam DDI	DiC-C	NSCLC	CYP3A induction
	TAK-788-1001	Food effect, relative BA	DiC-A/ DiC-B	HVs	SD PK

Source: summarized from figure 1 in pbpk-rpt-tak-788.pdf, BA: bioavailability, HVs: healthy volunteers, NSCLC: non-small cell lung cancer, Fa, fraction absorbed, fm: fraction metabolized, Indmax: maximal fold induction, fumic: unbound fraction in microsomes, SD: single dose

The details of key parameter assignment are described below. The final model input parameters are summarized in Table 60.

1. Mobocertinib clearance

Mobocertinib renal clearance (CLr) was reported in the range of 1.86 to 3.25 L/h (geometric mean value 2.5 L/h; Clinical Study TAK-788-1001; Single Ascending Dose). In vitro, mobocertinib is primarily metabolized by CYP3A4/5 with an estimated fmCYP3A4 of 85% based on the ketoconazole / troleandomycin chemical inhibition study in human liver microsomes (HLMs) (ARP588). In vitro recombinant human CYP (rhCYP) study suggested that CYP1A1, 2J2, 2C8, and CYP1A2, 2B6, 2C9, 2C19 and 2D6 were also involved in mobocertinib metabolism. Incubation with heart and lung microsomes suggested that mobocertinib may undergo extrahepatic metabolism. In the final model, the mobocertinib clearance consists of CLr (4%), CYP3A (89%), and additional CL (6%) (Figure 24) where the fmCYP3A was obtained by comparing the model predicted with the observed mobocertinib PK from in the absence and presence of itraconazole. Of note, the in vitro estimated fmCYP3A4 was 0.94 (based on rhCYP), or 0.85 (based on HLM inhibition) was close to the final fmCYP3A (0.89/(0.89+0.06) = 0.94) value (Figure 24). Among the 89% CYP3A, 52% is assigned to AP32960 formation (based on the human ADME study), 10% is assigned to AP32914 formation (based on PK following 160 mg QD mobocertinib), and 27% is assigned to other metabolites.

2. AP32960 clearance

The observed mobocertinib geometric mean clearance value of 55.9 L/h (Clinical Study TAK-788-1002) was also used as the AP32960 clearance because mobocertinib and AP32960 plasma concentration vs. time profiles showed approximately parallel elimination profiles. The CLr of AP32960 (1.25 L/hr) was calculated based on the unchanged drug excreted in urine (TKD-BCS-00362-R1). In vitro AP32960 was exclusively metabolized via CYP3A4, and a substrate of P-gp and BCRP. The fraction of AP32960 excreted unchanged in feces was 0.33 suggesting certain degree of biliary clearance (Report TKD-BCS-0362-R1). The final contribution from CYP3A4 and biliary excretion was 74% and 24%, respectively, based on comparing the predicted and observed AP32960 PK profiles in the absence and presence of itraconazole (Figure 23). The Applicant indicated that the lower biliary excretion in the model could be due to the possibility of back-conversion of downstream AP32960 metabolites to AP32960. To incorporate the inhibition

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effect on biliary clearance (potentially via P-gp/BCRP), the Applicant reduced the biliary CLint from 619 to 224 μl/min/10^6 cells. The AUC ratios were calculated using the AUCinh (AUC with the inhibitor, biliary CLint = 224 μl/min/10^6 cells) and AUC (AUC without the inhibitor, biliary CLint = 619 μl/min/10^6 cells).

3. AP32914 clearance

The observed mobocertinib geometric mean clearance value of 55.9 L/h (Clinical Study TAK-788-1002) was also used as the AP32914 clearance because mobocertinib and AP32914 plasma concentration-time profiles showed approximately parallel elimination profiles. In vitro, AP32914 is exclusively metabolized via CYP3A4. There is no renal or biliary elimination involved in AP32914 clearance. The final fmCYP3A4 (92%) (Figure 23) was determined based on comparing the AP32914 PK profiles in the presence and absence of itraconazole.

4. Unbound fraction in microsomes

The unbound fraction in microsomes (fumic) is used to estimate the in vitro intrinsic clearance (CLint) and the in vitro inhibition constant (Ki for competitive inhibition, and KI for TDI). Using the measured fumic values (<1%) resulted in 3-fold overprediction of the AP32960 formation clearance while using the in silico fumic (Table 57) resulted in the AP32960 formation clearance consistent with the observed in vivo values. Of note, the in silico fumic is calculated as fumic = 1/(([P]mic * 10^(0.646*logP-2.236))+1), where [P]mic is the microsomal protein concentration (mg/mL) used in the in vitro study.

5. CYP3A inhibition and induction parameters

In vitro, mobocertinib, AP32960 and AP32914 exhibited TDI and induction effects towards CYP3A4. The in vitro TDI parameters (kinact, and KI) corrected for the in silico fumic were directly applied in the model, and the in vitro Indmax (maximal induction evaluate) values were multiplied by 10 in order to capture the observed changes in midazolam PK, as well as the steady state PK of mobocertinib following 160 mg QD administration.

6. NSCLC population

The Sim-Cancer population was used to simulate the PK in the NSCLC population. Briefly, the cancer population has different levels of albumin, haematocrit, alpha acid glycoprotein, serum creatinine, OATP1B1/3 abundance, and MATE1 abundance compared with the healthy volunteers.

The final model input parameters are summarized in Table 60.

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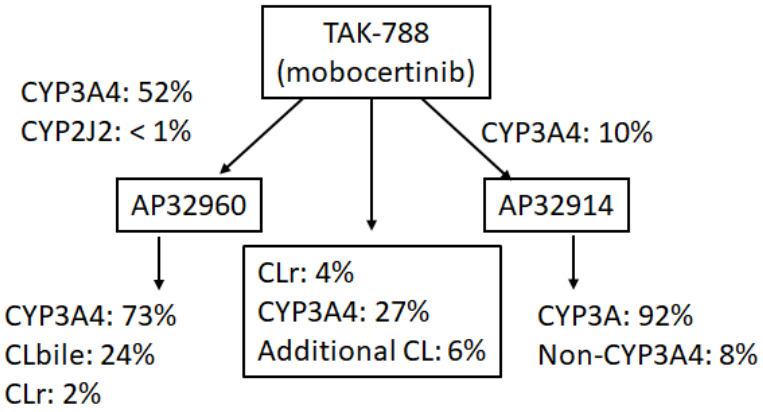
Figure 23: Illustration of clearance assignment for mobocertinib, AP32960, and AP32914 in the models.



Source: modified based on figure 6 in pbpk-rpt-tak-788.pdf

Table 60: PBPK model input parameters for mobocertinib, AP32960, and AP32914

Parameter	mobocertinib	References	AP32960	References	AP32914	References
MW	585.7		571.7		571.7	
logP	4.65	CMCCR-00484	3.41	CMCCR-00484	4 39	CMCCR-00484
Compound type	Diprotic base		Diprotic base		Diprotic base	
pKa	2.5, 9.13		2.64, 9.6		8.66, 2.74	
B:P	0.95	ARP569	1.01	ARP569	1.01	Assumed equal to AP32960
fup	0.007	ARP568	0.005	ARP568	0.011	ARP568
Distribution	Full PBPK		Full PBPK		Minimal PBPK	
Vss (L/kg)	12.8	Allometric scaling from dog PK data	12.7	Assumed equal to TAK-788 Vss	4	Optimized, AP32788-15-101
Absorption (First order)						
Caco-2 Papp ($x10^{-6}$ cm/s)	15	15ARIAP1R1				
Peff,man ($x10^{-4}$cm/s)	4.17	Predicted				
Qgut (L/h)	14.25	Predicted				
fugut	0.007	Equal to fup				
fa	0.92	TAK-788-1002; TKDBCS-00362-R1				
ka (h^{-1})	0.17	Optimized				
Tlag (hr)	1.5					
Elimination						
CL_R (L/h)	2.5	AK-788-1001	1.25	AK-788-1001	0	AK-788-1002
Additional Systemic CL (L/h)	3.2	Retrograde model: CL obtained from TAK-788-1002 (55.9 L/h); fa, 0.92; Fg, 1; CLR, 2.5 L/h; fm AP32960 formation, 0.52; fmAP32914				
CYP3A4 AP32960 formation CLint (µl/min/mg)	2247					
CYP2J2 AP32960 formation CLint (µl/min/mg)	37					
CYP3A4 AP32914 formation CLint (µl/min/mg)	439					

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Additional CYP3A4 CLint (μL/min/mg)	1669	formation, 0.10; fmCYP3A4, 0.88; TAK-788- 1006 Part 1 ITZ DDI	5569	CL assumed equal to TAK-788 (55.9 L/h). fmCYP3A4, 75%; TAK-788-1006 Part 1 ITZ DDI	3070	TAK-788-1002. CL assumed equal to TAK-788 and AP32960 (55 9 L/h). fmCYP3A4, 92%; TAK-788-1006 Part 1 ITZ DDI
Additional HLM Clint (μL/min/mg)					267	
Biliary CLint (μl/min/10^6 cells)			619			
Interaction						
CYP3A4 KI (μM)	58.9	RPT-03337 (testosterone)	7.29	RPT-03337 (testosterone)	10.11	RPT-03337 (testosterone)
CYP3A4 kinact (h^{-1})	1.98		0.66		1.08	
CYP3A4 fumic	0.08	Predicted	0.35	Predicted	0 113	Predicted
CYP3A4 IndC50 (μM)	0.61	1504071-Rev1	0.62	1504071-Rev1	1.49	1504071-Rev1
CYP3A4 Indmax	102	Optimization of based on TAK-788-1004	61.5	Optimization of based on TAK-788-1004	83.7	Optimization of based on TAK-788-1004
CYP3A4 fuinc	0.33	Predicted at 0.6 X 10^6 cells/mL	0.75	Predicted at 0.6 X 10^6 cells/mL	0.43	Predicted at 0.6 X 10^6 cells/mL
CYP3A4 Ki (μM)	5.8	ARP587. CYP3A4 - average of midazolam and testosterone values, corrected for Simcyp predicted fumic (0.84 and 0.72, respectively, at 0.05 and 0.1 mg/mL HLM, respectively)	9.9	ARP587. CYP3A4 - average of midazolam and testosterone values, corrected for Simcyp predicted fumic (0.92 and 0.96, respectively, at 0.05 and 0.1 mg/mL HLM, respectively)	10.1	ARP587. CYP3A4 - average of midazolam and testosterone values, corrected for Simcyp predicted fumic (0.84 and 0.72, respectively, at 0.05 and 0.1 mg/mL HLM, respectively)
CYP2B6 Ki (μM)	23.2		9.4			
CYP2B6 fumic	0.63		0.92			
CYP2C8 Ki (μM)	3.8		4.3			
CYP2C8 fumic	0.63		0.92			
CYP2C9 Ki (μM)	58.2		61.6			
CYP2C9 fumic	0.63		0.92			
P-gp Ki (μM)	35.9	TKD-BCS-00079-R1				
P-gp fuinc	1					
BCRP Ki (μM)	8.7					
BCRP fuinc	1					

Source: Tables 23-25 of pbpk-rpt-tak-788.pdf

Model validation

The model validation was performed by comparing model predicted with observed PK profiles following SD administration of 120 mg or 160 mg mobocertinib in HVs (Study TAK-788-1001), single ascending dose (SAD) and multiple ascending dose (MAD) PK in cancer patients (Study AP32788-15-101). The model predictions were also compared with the three DDI studies, with itraconazole, rifampin and midazolam. Of note, the itraconazole and midazolam DDI studies were also used for model calibration.

Model application

The model was then used to evaluate (1) the effect of strong CYP3A inhibitors (ketoconazole, and itraconazole), and inducer (rifampin), moderate CYP3A inhibitors (fluconazole, erythromycin, diltiazem, and verapamil), and inducer (efavirenz), and weak CYP3A inhibitor (cimetidine) on the

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steady state PK of mobocertinib, AP32960, AP32914 in cancer patients; and (2) the effect of mobocertinib and its metabolites on the PK of CYP2B6 (bupropion), CYP2C8 (repaglinide), CYP2C9 (warfarin), CYP3A4 (midazolam, and alprazolam), P-gp (digoxin, and dabigatran), and BCRP (sulfasalazine) substrates in cancer patients and HVs. As previously discussed, the use of PBPK analyses assessing the effect of mobocertinib (and its metabolites) on the PK of CYP2B6 and CYP2C9 substrates are not reviewed because the in vivo interaction potential is low based on the static model and correlation method calculations.

Results

1. **The PBPK model describes the PK profiles of mobocertinib and its metabolites, AP32960 and AP32914 following single- and multiple- dose administration of mobocertinib.**

In general, the model prediction was able to capture the observed Cmax and AUC for mobocertinib, AP32960, and AP32914 in the dose range between 5 mg and 180 mg with the predicted / observed ratios within 0.6-1.5 except for the day 29 PK following 80 mg QD where the predicted Cmax and AUC for mobocertinib were about 2-fold of the observed values (Table 61). Given the model was able to describe most of the clinical PK dataset of mobocertinib and its metabolites under various dosing scenarios, the PBPK model can be considered able to describe the PK profiles of mobocertinib and its metabolites. In addition, the reviewer simulated the PK using the 'healthy volunteers' population. The differences in simulated PK are generally less than 10% using the 'healthy volunteers' vs. the 'cancer' populations.

Table 61: Summary of predicted and observed PK for mobocertinib, AP32960, and AP32914 following single- and multiple- dose administration of mobocertinib.

Dose (mg)	Day	Source	Mobocertinib		AP32960		AP32914	
			Cmax (ng/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	AUC0-24 (ng*hr/mL)
5	1	Obs (N=4)	2.27	28.3	0.63	8.4	0.22	2.6
		Pred	2.06	26	0.7	10	0.17	2.52
		Pred / Obs	**0.91**	**0.92**	**1.11**	**1.19**	**0.77**	**0.97**
	29	Obs (N=2)	2.15	36	0.89	15.1	0.25	3.9
		Pred	3.16	45	1.26	21	0.24	3.91
		Pred / Obs	**1.47**	**1.25**	**1.42**	**1.39**	**0.96**	**1.00**
10	1	Obs (N=5)	5.37	62.3	1.97	26.2	0.44	5.4
		Pred	3.75	48	1.34	19	0.31	4.57
		Pred / Obs	**0.70**	**0.77**	**0.68**	**0.73**	**0.70**	**0.85**
	29	Obs (N=2)	5.77	99.8	2.32	44.2	0.34	5.9
		Pred	5.59	75	2.26	35	0.42	6.54
		Pred / Obs	**0.97**	**0.75**	**0.97**	**0.79**	**1.24**	**1.11**
20	1	Obs (N=5)	8.79	99.2	4	42.8	0.76	9

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		Pred	8.08	103	2.88	41.4	0.66	9.73
		Pred / Obs	**0.92**	**1.04**	**0.72**	**0.97**	**0.87**	**1.08**
	29	Obs (N=4)	7.7	105	3.75	57.3	0.77	11.1
		Pred	11.1	154	4.54	72.4	0.84	13.5
		Pred / Obs	**1.44**	**1.47**	**1.21**	**1.26**	**1.09**	**1.22**
40	1	Obs (N=6)	20.2	250	7.1	87.9	1.45	18.8
		Pred	17.2	225	6	88.9	1.39	21.1
		Pred / Obs	**0.85**	**0.90**	**0.85**	**1.01**	**0.96**	**1.12**
	29	Obs (N=4)	19.3	295	10.3	164	1.4	22.2
		Pred	23.3	321	9.63	153	1.75	28.1
		Pred / Obs	**1.21**	**1.09**	**0.93**	**0.93**	**1.25**	**1.27**
80	1	Obs (N=7)	33.3	386	14.9	170	2.35	29.2
		Pred	34	445	11.8	175	2.79	42
		Pred / Obs	**1.02**	**1.15**	**0.79**	**1.03**	**1.19**	**1.44**
	29	Obs (N=3)	22.4	321	15.6	231	1.97	29.3
		Pred	47.2	654	20.2	322	3.53	57.6
		Pred / Obs	**2.11**	**2.04**	**1.29**	**1.39**	**1.79**	**1.97**
120	1	Obs (N=26)	49.3	599	25.8	294	3.16	43.3
		Pred	51.1	663	18	267	4.12	62.5
		Pred / Obs	**1.04**	**1.11**	**0.70**	**0.91**	**1.30**	**1.44**
	29	Obs (N=14)	52.9	772	32.3	477	3.4	51.5
		Pred	58.7	830	25.9	416	4.56	73.4
		Pred / Obs	**1.11**	**1.08**	**0.80**	**0.87**	**1.34**	**1.43**
180	1	Obs (N=4)	86.9	1055	40.6	487	6.31	78.9
		Pred	81	990	28.4	401	6.3	93.1
		Pred / Obs	**0.93**	**0.94**	**0.70**	**0.82**	**1.00**	**1.18**
	29	Obs (N=1)	64.8	768	39.9	531	5.3	73.3
		Pred	77.3	1006	34.6	512	6.02	88.8
		Pred / Obs	**1.19**	**1.31**	**0.87**	**0.96**	**1.14**	**1.21**

Source: Tables 42-55 of pbpk-rpt-tak-788.pdf

2. The PBPK model predicts that a moderate CYP3A inhibitor can increase total combined molar exposure of mobocertinib, AP32960 and AP32914 by approximately 100%-200%.

In general, the model was able to capture the PK and PK changes for mobocertinib when was co-administered with itraconazole (Table 62).

The factors affecting the DDI evaluation with CYP3A inhibitors are discussed below in detail.

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(1). The effect of biliary clearance inhibition on DDI prediction
The Applicant incorporated a semi-mechanistic P-gp/BCRP-mediated biliary clearance in the AP32960 model to capture the observed PK change in the presence and absence of itraconazole. Some CYP3A inhibitors may also inhibit P-gp (such as itraconazole, ketoconazole, and verapamil). Without considering the effect of biliary clearance inhibition, the estimated AUCR of AP32960 (the AUC ratio) in the presence and absence of ketoconazole or itraconazole was approximately 2-fold; while considering the effect of biliary clearance inhibition, the estimated AUCR was approximately 3.5-fold. Overall, the difference does not have much impact on the total molar exposure change because mobocertinib is the major moiety (65%, and 85% in the absence and presence of itraconazole, respectively) of the total molar exposure.

(2). The induction effect of mobocertinib on itraconazole
Mobocertinib has weak induction effect on midazolam (a sensitive CYP3A substrate) at the dose level of 160 mg QD (see the discussion on the effect of mobocertinib on the PK of a sensitive CYP3A substrate for details). Itraconazole is a CYP3A substrate. The DDI study with itraconazole was conducted at mobocertinib dose of 20 mg QD. Therefore, the induction effect on itraconazole is expected to be low which was confirmed by simulations.

(3). The effect of unbound fraction on the total combined molar exposure calculation
In the combined molar exposure calculation, the same pharmacological potency was assumed and the unbound fraction in plasma (fup) for each moiety was not consider. The impact of fup on the calculated total combined molar exposure was evaluated and the differences in CmaxR or AUCR are generally less than 5% comparing the total combined molar exposure corrected vs. uncorrected for fup in the case of mobocertinib and its metabolites. Therefore, the combined molar exposure uncorrected for fup is used for dose adjustment considerations. Of note, the Applicant also calculated combined molar Cmax using the parameter for each moiety. To estimate the combined molar Cmax, the total molar concentrations should be first estimated for each time point, and the combined molar Cmax is estimated based on the total molar concentration vs. time curve because the Tmax (i.e., Cmax) of each moiety does not occur at the same time.

Table 62: Summary of predicted and observed PK and PK changes for mobocertinib, AP32960, and AP32914 in the absence and presence of itraconazole.

	Moiety	Mobocertinib (20 mg)		Mobocertinib (20 mg) + Itraconazole		Mobocertinib + Itraconazole / Mobocertinib	
		Cmax (ng/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	AUCinf (ng*hr/mL)	CmaxR	AUCR
Observed	Mobocertinib	5.52	106	21.1	892	3.83	8.43
	AP32960	2.11	48.8	1.43	132	0.68	2.70

	AP32914	0.35	7.16	0.22	18.7	0.57	2.61
	Combined molar exposure (nM*hr)	NA	278.87	NA	1786.55	NA	6.27
Predicted	**Mobocertinib**	6.78	139.00	20.2	1258	2.98	9.05
	AP32960	2.42	66	1.3	168	0.54	2.55
	AP32914	0.58	12	0.4	33	0.69	2.75
	Combined molar exposure (nM*hr)	NA	373.76	NA	2499.42	NA	6.69
Pred / Obs	**Mobocertinib**	1.23	1.31	0.96	1.41	0.78	1.07
	AP32960	1.15	1.35	0.91	1.27	0.79	0.94
	AP32914	1.66	1.68	1.82	1.76	1.21	1.05
	Combined molar exposure (nM*hr)	NA	1.34	NA	1.40	NA	1.07

Source: Tables 12, 15, 18 of pbpk-rpt-tak-788.pdf; NA: not applicable; The combined molar exposure was calculated using the equation: Combined molar exposure (AUC) = exposure (mobocertinib) / MW (mobocertinib) + exposure (AP32960) / MW (AP32960) + exposure (AP32914) / MW (AP32914); CmaxR: Cmax ratios of a substrate in the presence and absence of a perpetrator; AUCR: AUC ratios of a substrate in the presence and absence of a perpetrator.

The Applicant evaluated the effect of moderate (erythromycin, fluconazole, diltiazem, and verapamil) and weak (cimetidine) CYP3A inhibitors on the PK of mobocertinib, AP32960, and AP32914. The reviewer noticed that the Simcyp version 18 erythromycin model over-predicted its effect on midazolam (observed AUCR of 4.42 vs. predicted AUCR of 7.45) although it could reasonably capture its effects on triazolam and alprazolam. An information request was sent to the Applicant. The Applicant responded that the overprediction was resolved in Simcyp V20 and conducted additional DDI simulations with verapamil (and its inhibitory metabolite norverapamil) and diltiazem (and its inhibitory metabolite demethyldiltiazem). The reviewer noticed that the diltiazem model underpredicted its effect on midazolam (observed AUCR of 3.75 vs. predicted AUCR of 2.03) although it could reasonably capture its effect on triazolam (observed AUCR of 2.83 vs. predicted AUCR of 2.02).

Overall, the model predicted that a strong CYP3A inhibitor (such as itraconazole, or ketoconazole) may increase mobocertinib and the combined molar exposure by approximately 6-fold and 5-fold, respectively (Table 63). The model predicted that a moderate CYP3A inhibitor may increase mobocertinib and the combined molar exposure approximately by 2.4 to 4-fold, and 2 to 3-fold, respectively (Table 63). Of note, verapamil is also a P-gp inhibitor and its effect on AP32960 biliary clearance reduction was not considered in the simulation.

Table 63: Predicted (Cmax and AUC) changes in mobocertinib, AP32960, AP32914 exposures, and combined molar exposure at steady state when mobocertinib (160 mg QD) is co-administered with a CYP3A inhibitor

Perpetrator (dose)	Mobocertinib	AP32960[a]	AP32914	Combined molar exposure

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	CmaxR	AUCtauR	CmaxR	AUCtauR	CmaxR	AUCtauR	CmaxR	AUCtauR
Itraconazole 200 mg QD	4.99	6.23	2.56	3.37	2.63	3.28	NA	5.19
Ketoconazole 400 mg QD	4.9	5.71	2.55	3.21	2.42	2.84	NA	4.74
Erythromycin 500 mg TID	2.14	2.42	1.38	1.61	1.85	2.16	NA	2.16
Fluconazole 200 mg QD	2.3	2.61	1.55	1.84	1.99	2.31	NA	2.35
Fluconazole 400 mg QD[b]	3.15	3.89	1.70	2.16	2.45	3.07	NA	3.29
Diltiazem 120 mg BID	2.34	2.69	1.49	1.77	2.00	2.37	NA	2.38
Verapamil 80 mg TID	2.88	3.45	1.56	1.90	2.32	2.84	NA	2.91
Cimetidine 400 mg TID	1.19	1.18	1.1	1.11	1.12	1.16	NA	1.16

Source: Table 67 of pbpk-rpt-tak-788.pdf, and updated output files submitted by the Applicant; [a]Itraconazole and ketoconazole simulations incorporated a change in AP32960 biliary CLint in addition to CYP3A4 inhibition; [b]mobocertinib 80 mg QD; CmaxR: Cmax ratios of a substrate in the presence and absence of a perpetrator; AUCtauR: steady state AUC0-24 ratios of a substrate in the presence and absence of a perpetrator

Simulations were also conducted following 40 mg or 80 mg mobocertinib in the presence of various moderate CYP3A inhibitors. The simulated steady state combined molar AUC0-24 values were compared with that following 160 mg QD mobocertinib alone (Figure 24). In majority of the cases, the predicted steady state combined molar AUC0-24 following 40 mg mobocertinib in the presence of a moderate CYP3A is slightly lower than the steady state combined molar AUC0-24 following 160 mg QD mobocertinib alone; while the predicted steady state combined molar AUC0-24 following 80 mg mobocertinib in the presence of a moderate CYP3A is higher than the steady state combined molar AUC0-24 following 160 mg QD mobocertinib alone but largely overlap.

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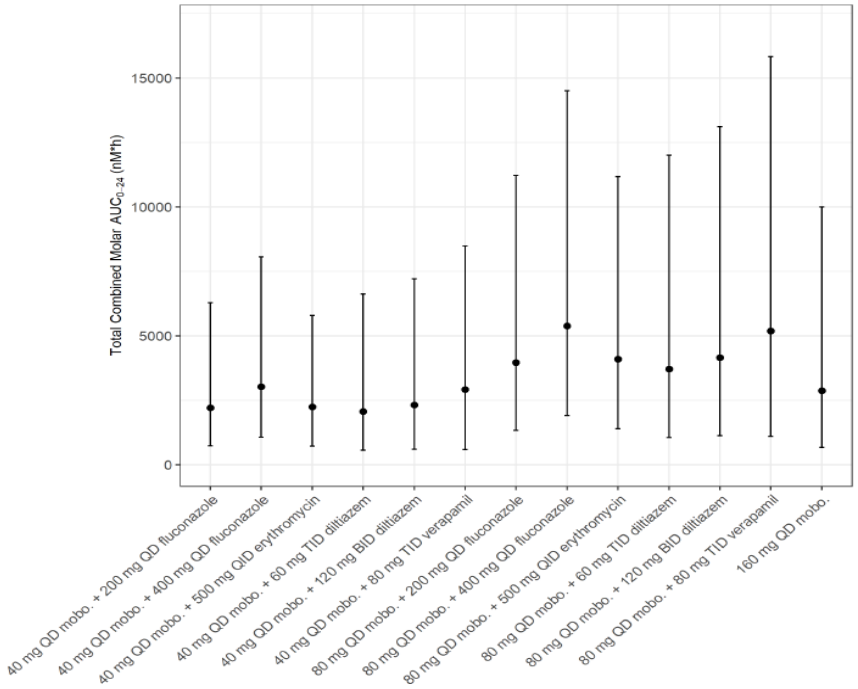
Figure 24: Comparison of simulated geometric mean steady state combined molar AUC0-24 following 40 mg or 80 mg mobocertinib in the presence of various moderate CYP3A inhibitors with simulated geometric mean steady state combined molar AUC0-24 following 160 mg QD



Source: Figure 2d in the response to FDA IR dated 16 June 2021 submitted on June 21, 2021; AUC0-24: area under the concentration-time curve from time 0 to 24 hours; BID: twice daily; mobo: mobocertinib; QD: once daily; QID: 4 times daily TID: 3 times daily; Circles represent the geometric mean and error bars represent the minimum and maximum for the total simulated population of 200 (10 trials each containing 20 patients).

3. The PBPK analysis predicts that a moderate CYP3A inducer can decreased the combined molar exposure of mobocertinib, AP32960 and AP32914 by approximately 60%.

In general, the model was able to capture the PK for mobocertinib, and AP32960, and over-predicted the PK for AP32914 (approximately 2-fold of the observed PK) (Table 64). The model under-estimated the effect of rifampin on the PK of mobocertinib even a rifampicin CYP3A4 Indmax value of 37 was used (Table 64). Nevertheless, the predicted effect still falls into the strong DDI effect category (>80% decrease in the exposure of the substrate).

Table 64: Summary of predicted and observed PK and PK changes for mobocertinib, AP32960, and AP32914 in the absence and presence of rifampin

	Moiety	Mobocertinib (160 mg)		Mobocertinib (160 mg) + Rifampin		Mobocertinib + Rifampin / Mobocertinib	
		Cmax (ng/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	AUCinf (ng*hr/mL)	CmaxR	AUCR
Observed	Mobocertinib	70	1360	3.65	56.9	0.05	0.04
	AP32960	26.9	681	4.79	55.8	0.18	0.08
	AP32914	2.29	45.2	0.28	3.59	0.12	0.08
	Combined molar exposure (nM*hr)	NA	3592.28	NA	201.04	NA	0.06
Predicted	Mobocertinib	57.9	1101	5.76	63.8	0.10	0.06
	AP32960	21.2	532	4.48	56.6	0.21	0.11
	AP32914	4.74	96.7	0.5	6.1	0.11	0.06
	Combined molar exposure (nM*hr)	NA	2979.53	NA	218.61	NA	0.07
Pred / Obs	Mobocertinib	0.83	0.81	1.58	1.12	1.91	1.39
	AP32960	0.79	0.78	0.94	1.01	1.19	1.30
	AP32914	2.07	2.14	1.79	1.70	0.86	0.79
	Combined molar exposure (nM*hr)	NA	0.83	NA	1.09	NA	1.31

Source: Tables 39-41 of pbpk-rpt-tak-788.pdf; NA: not applicable; The combined molar exposure was calculated using the equation: Combined molar exposure (AUC) = exposure (mobocertinib) / MW (mobocertinib) + exposure (AP32960) / MW (AP32960) + exposure (AP32914) / MW (AP32914); CmaxR: Cmax ratios of a substrate in the presence and absence of a perpetrator; AUCR: AUC ratios of a substrate in the presence and absence of a perpetrator

When mobocertinib (160 mg QD) was administered with efavirenz, a moderate CYP3A inducer, the steady state AUC of mobocertinib, AP32960, AP32914, and the combined molar exposure were predicted to be decreased by approximately 60% (Table 65). The effect of different models (default, additive, and multiplicative) to simulate multiple inducers on the DDI prediction was evaluated because mobocertinib is a weak CYP3A inducer. Among the three models, the default model predicted (Table 65) the lowest DDI magnitude, and the multiplicative model predicted the highest DDI magnitude (data not shown). The difference in the predicted magnitude was not large and all the models predicted more than 50% decrease in the mobocertinib, AP32960, AP32914, and the combined molar exposures when mobocertinib is co-administered with efavirenz.

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Table 65: Predicted (Cmax and AUC) changes in mobocertinib, AP32960, AP32914 exposures, and combined molar exposure at steady state when mobocertinib (160 mg QD) is co-administered with a strong or moderate CYP3A inducer

Perpetrator (dose)	Mobocertinib		AP32960		AP32914		Combined molar exposure	
	CmaxR	AUCtauR	CmaxR	AUCtauR	CmaxR	AUCtauR	CmaxR	AUCtauR
Rifampin (600 mg QD)	0.1	0.07	0.17	0.11	0.1	0.07	NA	0.08
Efavirenz (600 mg QD)	0.44	0.4	0.52	0.45	0.47	0.41	NA	0.42

Source: Table 67 of pbpk-rpt-tak-788.pdf; the default model was used to simulate multiple inducers; NA: not applicable; The combined molar exposure was calculated using the equation: Combined molar exposure (AUC) = exposure (mobocertinib) / MW (mobocertinib) + exposure (AP32960) / MW (AP32960) + exposure (AP32914) / MW (AP32914); CmaxR: Cmax ratios of a substrate in the presence and absence of a perpetrator; AUCtauR: steady state AUC0-24 ratios of a substrate in the presence and absence of a perpetrator

4. **PBPK analyses suggests that the observed weak effects of mobocertinib on the PK of CYP3A substrates mainly come from the induction effect.**

In vitro, mobocertinib, AP32960, and AP32914 are competitive, and time-dependent inhibitors, and inducers of CYP3A. To capture the effect of mobocertinib on midazolam (Table 66) and itself (steady state PK, Table 67), a factor of 10 was applied to in vitro maximal induction effect (Indmax) (Table 60). The inhibition parameters came from in vitro studies except for the unbound fraction in microsomes (fumic) where the in silico values were used (Table 57). This set of parameters was able to capture the observed AUC change in midazolam although the model under-predicted the PK of midazolam (Table 66). Of note, in the midazolam DDI simulation, the inhibition effect of metabolite, AP32914, was not included. The impact on the result of midazolam DDI simulation is expected to be minimal due to the low exposure of AP32914.

Comparing the historic in vitro average Indmax (47) and IndC50 (0.33 µM) values by rifampin on the same three lots of hepatocytes used for mobocertinib induction study with the Indmax (37) and IndC50 (0.32 µM) values used in the rifampin model, the in vitro Indmax is slightly higher. However, the in vitro Indmax for mobocertinib model was increased by 10-fold to capture the observed effect of mobocertinib on midazolam. A 10-fold factor is needed probably is because the mobocertinib enterocyte concentrations are underestimated (see the discussion on the effects of mobocertinib on the PK of a P-gp substrate).

As the observed effect of mobocertinib on midazolam is a net effect, the Applicant was asked to address the impact of inhibitory parameters on the DDI prediction. The Applicant responded that based on the in-house experience, using data derived from liver microsomes, corrected from binding using measured values of fumic generally overpredicted TDI (Responses to FDA Information Request dated 28 May 2021 submitted on 09 June 2021). The Reviewer searched in vitro inhibitory parameters for time-dependent inhibitors,
atazanavir, clarithromycin, diltiazem, erythromycin, esomeprazole, fluoxetine, mirabegron, omeprazole, paroxetine, ritonavir, ticlopidine, and verapamil in UW DIDB, and compared the in

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vitro KI (the concentration which produces the half maximal rate of inactivation) and Kinact (the maximum rate constant for inactivation) values with those being used in the corresponding models. In general, the KI and Kinact values in the models are within the range of reported values, and both values are closer to the lower ends of the reported in vitro ranges. Simulations were also conducted to evaluate the impact of inhibition on the overall effect on midazolam. Based on the simulations using the input parameters in Table 60, TDI does not have impact on the overall effect on midazolam. Lowering the inhibition constants (Ki for competitive inhibition, and Kapp for TDI) by 10-fold, the predicted AUCR of midazolam became 0.81. Turning off the induction effect and lowering the inhibition constants by 10-fold, the predicted AUCR of midazolam was 1.59.

These analyses suggested that the net effect of mobocertinib on midazolam reflects the induction effect and appears to be weak. CYP3A inducers may also inducer CYP2C enzymes (CYP2C8, CYP2C9, and CYP2C19). The in vitro induction study suggested the induction potential for mobocertinib toward CYP2C8 and CYP2C9 is minimal. A search in the University of Washington Drug Interaction Database (UW DIDB) suggested that in general, the CYP2C induction effects are weaker or similar compared with the CYP3A induction for a CYP3A inducer. Therefore, the effect of mobocertinib on the PK of CYP2C substrate is expected to be weak.

Table 66: Summary of predicted and observed PK and PK changes for midazolam in the absence and presence of mobocertinib

Midazolam dose	Southe	Midazolam		Midazolam + Mobocertinib (160mg QD)		Midazolam + Mobocertinib / Midazolam	
		Cmax (ng/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	AUCinf (ng*hr/mL)	CmaxR	AUCR
Oral (3mg)	Observed	17	58.3	17.5	39	1.03	0.68
	Predicted	11.95	39.11	8.36	24.53	0.70	0.63
	Pred/Obs	0.70	0.67	0.48	0.63	0.68	0.92
IV (1mg/5min)	Observed	70.8	90.4	92.2	71.6	1.3	0.84
	Predicted	22.89	50.09	22.92	43.70	1.00	0.87
	Pred/Obs	0.32	0.55	0.25	0.61	0.77	1.04

Source: observed data: TAK-788-1004 CSR addendum PK headline data (Figure 3a), predicted oral midazolam PK and DDI: Tables 64 of pbpk-rpt-tak-788.pdf, predicted IV midazolam PK and DDI: reviewer's simulations using submitted model file 'perp-app-ddi-mdz-md-indmax10.wksz' with modified dosing regimens according to study 1004; mobocertinib dose: 160 mg QD days 3 to 30, midazolam: 3mg oral days 1 and 24, 1 mg IV for 5min on day 2 and 25; CmaxR: Cmax ratios of a substrate in the presence and absence of a perpetrator; AUCR: AUC ratios of a substrate in the presence and absence of a perpetrator

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Table 67: Summary of predicted and observed PK for mobocertinib, AP32960, and AP32914 following single- and multiple- dose administration of 160 mg mobocertinib QD.

Dose (mg)	Day	Source	Mobocertinib		AP32960		AP32914	
			Cmax (ng/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	AUC0-24 (ng*hr/mL)
160	1	Obs (N=138)	77.9	972	33.3	423	4.53	60.1
		Pred[a]	67.91	879.07	23.99	355.96	5.46	82.89
		Pred / Obs	0.87	0.90	0.72	0.84	1.20	1.38
	29	Obs (N=70)	70.4	951	40.6	572	4.96	68.1
		Pred[b]	73.25	1031.55	33.58	536.66	5.70	92.23
		Pred / Obs	1.04	1.08	0.83	0.94	1.15	1.35

Source: Tables 2.b-2.d of summary of clinical pharmacology, [a] reviewer's simulation using the Applicant's model, [b]sdy101-tak788-160mg-qd-d29-indmax10 xlsx

5. **The PBPK analysis suggests there is no clinically meaningful effect of mobocertinib on the PK of CYP2C8 substrates.**

The Applicant evaluated the effect of mobocertinib on repaglinide (a CYP2C8 and CYP3A4 substrate). Mobocertinib has weak induction effect on CYP3A. The reviewer conducted simulations by turning off the effect of mobocertinib on CYP3A, and further lower the CYP2C8 Ki value by 100-fold. The simulated increase in repaglinide exposure is less than 5%. The reviewer also conducted DDI simulations with rosiglitazone (a CYP2C8 and CYP2C9 substrate). The simulation suggested that the increase in rosiglitazone exposure is less than 5% even the CYP2C8 Ki value was lowered by 100-fold. Therefore, the effect of mobocertinib on the PK of a CYP2C8 substrate is minimal.

6. **The PBPK analysis suggests the effects of mobocertinib on the PK of a P-gp substrate is expected to be minimal.**

In Caco-2 cell monolayers, mobocertinib inhibited P-gp-mediated bidirectional transport of digoxin with an IC50 of 36.1 μM (Tabulated Summary 2.6.5.15A; Report TKD-BCS-00079-R1). The static model suggested there is a potential P-gp mediated interaction in the gut (Igut/IC50 = 30 > 10) but not at the systemic level (Imax,u/IC50 < 0.1). Therefore, this review evaluates the adequacy of the submitted PBPK analyses to predict the effects of mobocertinib on the PK of P-gp substrates in the gut.

To evaluate the effect of mobocertinib on the PK P-gp substrates, digoxin and dabigatran etexilate models were developed, validated, and applied. Both the digoxin and dabigatran etexilate models incorporate the Advanced Dissolution, Absorption and Metabolism (ADAM) model. P-gp is incorporated in the GI tract. Dabigatran etexilate is a P-gp substrate and its active metabolite, dabigatran, is not a P-gp substrate. The effects of P-gp inhibitors on the dabigatran etexilate are assessed by the changes in dabigatran plasma exposure. The absorption

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model is a first order absorption model for the P-gp perpetrators, clarithromycin, ketoconazole, ritonavir and quinidine, and an ADAM model for ritonavir and verapamil. For a first order absorption model, the unbound portal vein concentration (fugut*Cpv) of the perpetrators is the driving force for P-gp mediated interactions in the gut. The digoxin and dabigatran etexilate model validations are summarized in Table 68 and Table 69 respectively. In addition to the validation submitted by the Applicant, the reviewer searched DDI studies involving digoxin and dabigatran etexilate in the UW DIDB and conducted additional model validation (Table 68 and Table 69).

In general, these validations suggested that the digoxin and dabigatran models can capture >25% increase in Cmax and AUC. Slight underprediction of the clarithromycin and quinidine effects on digoxin could be due to the lack of interaction at the systemic level (such as kidney).

Table 68: Summary of digoxin model validation

Perpetrator	Perpetrator dose	Substrate dose	pred. CmaxR	pred. AUCR	obs. CmaxR	obs. AUCR	Pred / Obs CmaxR	Pred/Obs AUCR	Source of simulation	Source of observed
Clarithromycin	250 mg BID (3 days)	0.75 mg SD Day3 30 min after	1.15	1.1	1.83	1.64	0.63	0.67	Reviewer	PubMed 12848773
	500 mg BID (7 days)	0.4 mg SD Day7	1.4	1.24	1.48	1.35	0.95	0.92	Reviewer	PubMed 16221754
	500 mg BID (7 days)	0.5 mg SD Day7	1.4	1.24	1.95	1.57	0.72	0.79	Reviewer	PubMed 17079360
	500 mg BID (7 days)	0.25 mg SD Day3	1.38	1.25	1.75	1.68	0.79	0.74	Reviewer	PubMed 18214850
Quinidine*	not reported	not reported	1.97	1.55	1.75	1.77	1.13	0.88	Reviewer	PubMed 6832200
Ritonavir	200mg TID day1, 300mg BID days 2-7 and 400mg BID days 8-15, and 400 mg on day 16	0.5 mg on day 16	1.65	1.32	1.16	1.37	1.42	0.96	Applicant	Applicant
			1.62	1.38			1.40	1.01	Reviewer	Applicant
Verapamil / Norverapamil	80mg PO, BID for 4 days and 80mg PO, TID for the following 10days	0.25 mg BID for 14 days	1.61	1.47	1.44	1.5	1.12	0.98	Applicant	Applicant
			1.55	1.51			1.08	1.01	Reviewer	Applicant

* simulated dose: quinidine 600 mg BID for 10 days, digoxin 0.4 mg SD on day 8. The reviewer's simulation was conducted using Simcyp V20, healthy subjects, one trial with 20 subjects.

Table 69: Summary of dabigatran model validation

Perpetrator	Perpetrator dose	Substrate dose	pred. CmaxR	pred. AUCR	obs. CmaxR	obs. AUCR	Pred / Obs CmaxR	Pred/Obs AUCR	Source of Simulation	Source of Observed
Clarithromycin	500 mg BID for 4 days (7 doses)	300 mg SD (Day 4)	1.5	1.44	1.6	1.49	0.94	0.97	Applicant	Applicant
			1.66	1.6			1.04	1.07	Reviewer	Applicant
	500 mg BID for 5 days	300 mg SD (Day 5)	1.54	1.48	1.79	2.14	0.86	0.69	Applicant	Applicant
			1.69	1.61			0.94	0.75	Reviewer	Applicant
Ketoconazole	400 mg QD for 8 days	150 mg SD (Day 8)	1.94	1.83	2.49	2.53	0.78	0.72	Applicant	Applicant
	400 mg QD for 8 days	150 mg SD (Day 8)	2.63	2.45			1.06	0.97	Reviewer	Applicant
Quinidine	200 mg every 2h for 5 doses on Day 3	150 mg BID for 3 days	1.65	1.54	1.56	1.53	1.06	1.01	Applicant	Applicant
			2.52	2.38			1.62	1.56	Reviewer	Applicant
Ritonavir	100 mg QD days5-26	150 mg SD Day26	1.22	1.21	1.1	1.2	1.11	1.01	Reviewer	PubMed 28848011
Verapamil / Norverapamil	120 mg SD	150 mg SD (co-administration)	2.62	2.33	2.29	2.08	1.14	1.12	Applicant	Applicant
			3	2.68			1.31	1.29	Reviewer	Applicant
		150 mg SD (1h after verapamil)	2.4	2.15	2.79	2.43	0.86	0.88	Applicant	Applicant
			2.74	2.47			0.98	1.02	Reviewer	Applicant

The Ki values are incorporated in the Simcyp V20 library files except for ketoconazole which is provided in the dabigatran etexilate model validation file.

Two critical aspects to the overall DDI prediction are the perpetrator concentration at the site of interaction, and the inhibition constant (Ki). For the first order absorption model, the unbound portal vein concentration (fugut*Cpv) is the relevant perpetrator concentration. The reviewer compared the maximal unbound portal vein concentration (fugut*Cpv,max) with the estimated GI luminal concentration (using dose / 250mL) or the solubility for the perpetrators in Table 68 and Table 69. For poorly soluble drugs (clarithromycin, ketoconazole, and ritonavir), the maximal unbound portal vein concentrations are much higher than solubility. For drugs with moderate to high solubility, e.g, quinidine, the maximal unbound portal vein concentration is much lower than solubility or the estimated GI luminal concentration. Mobocertinib is a highly soluble drug, and the estimated GI luminal concentration is 0.64 mg/mL (160mg/250mL). The maximal unbound portal vein concentration is approximately 3E-6 mg/mL. For a highly soluble drug with high protein binding, a first order absorption model may significantly underestimate the perpetrator's concentration at the site of interaction.

The other important aspect of the DDI prediction is the inhibition constants (Ki). It has been reported that the in vitro Ki values generally underestimate the observed transporter mediated DDIs. The differences between the in vitro Ki values and the Ki values used in each perpetrator model provide basis for the range of sensitivity analysis on Ki. In the response to FDA's

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information request received on June 9, 2021, the Applicant provided ranges of in vitro Ki values for clarithromycin, ritonavir, and verapamil. In addition, the reviewer searched in vitro IC50 values for clarithromycin, ketoconazole, quinidine, ritonavir, and verapamil/norverapamil. The comparisons of in vitro Ki and model Ki values are summarized in Table 67.

The in vitro IC50 values vary largely depending on the cell culture, substrate, experimental conditions, and data analysis methods (Table 70). The reviewer included the IC50 values measured in Caco2 using dabigatran etexilate, or digoxin as the substrate. The Ki values were estimated using IC50/2. For clarithromycin, ketoconazole, quinidine, and verapamil, the in vitro and in vivo fold differences in Ki were less than 60-fold. For ritonavir, the in vitro and in vivo differences in Ki could be as large as 400-fold. Of note, ritonavir has the least impact on the PK of digoxin and dabigatran compared to the other P-gp inhibitors (clarithromycin, ketoconazole, quinidine, and verapamil/norverapamil) and has complicated interaction mechanisms on P-gp.

There was one study reported the in vitro IC50 for norverapamil. In the model, both verapamil and norverapamil have the potential to inhibit P-gp. The reviewer conducted DDI simulations to evaluate the contribution of verapamil and norverapamil to the overall simulated DDI effect, respectively. The results suggested that the DDI effect caused by verapamil or norverapamil alone was only slightly lower than the overall effect.

Table 70: Comparison of in vitro and model Ki values for P-gp perpetrators

Perpetrator	in vitro Ki (uM)	in vitro substrate	model Ki (uM)	Fold difference	In vitro Ki reference
Clarithromycin	8.55-14	dabigatran etexilate	4	2-3.5	DIDB database, Caco2, IC50/2
	1.32-32.7	digoxin		0.33 - 8.2	Applicant IR response
	2.1-33	digoxin		0.5-8.25	DIDB database, Caco2, IC50/2
ketoconazole	1.7	dabigatran etexilate	0.059	29	DIDB database, Caco2, IC50/2
	0.21-2.3	digoxin		3.6-39	DIDB database, Caco2, IC50/2
Quinidine	16.5	dabigatran etexilate	0.64	26	DIDB database, Caco2, IC50/2
	0.1-10.5	digoxin		0.16-16	DIDB database, Caco2, IC50/2
Ritonavir	13	dabigatran etexilate	0.03	433	DIDB database, Caco2, IC50/2
	1.22-4.81	digoxin		41-160	Applicant IR response
	0.75-5	digoxin		25-167	DIDB database, Caco2, IC50/2
Verapamil / Norverapamil	0.185-9.14	digoxin	0.16 / 0.04	1.2-57	Applicant IR response
	0.03-8.4/0.015	digoxin		0.2-53/4	DIDB database, Caco2, IC50/2

To account for the underprediction of the perpetrator concentration at the site of interaction, the Applicant developed an ADAM model for mobocertinib and re-evaluated the effect of mobocertinib on the PK of P-gp substrates in response to FDA's information

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request. The Applicant lowered in vitro Ki value by 15-fold to account for potential differences between in vitro and in vivo inhibition constants. To account for the uncertainty in in vitro inhibition constant, the reviewer further lowered the Ki value by 500-fold, and increased fugut to 1 based on the Applicant's ADAM model. This model predicted less than 20% increase in exposures of digoxin and dabigatran. Therefore, the effect of mobocertinib on the PK of a P-gp substrate is expected to be low.

(b) (4)

Conclusions

The Division of Pharmacometrics has reviewed the Applicant's PBPK analysis for mobocertinib and its metabolites, AP32960, and AP32914, and concluded the following.

- The PBPK analysis is adequate to evaluate the effects of CYP3A inhibitors on the PK of mobocertinib. The model predicted that a strong CYP3A inhibitor (such as itraconazole and ketoconazole) may increase the steady state combined molar exposure of mobocertinib, AP32960, and AP32914 by approximately 400%; a moderate CYP3A inhibitor may increase the combined molar exposure by approximately 100%-200%.
- The PBPK analysis is adequate to evaluate the effects of CYP3A inducers on the PK of mobocertinib. The model predicted that a strong CYP3A inducer, rifampin, may decrease the steady state combined molar exposure of mobocertinib, AP32960, and AP32914 by more than 90%; a moderate CYP3A inducer, efavirenz, may decrease the combined molar exposure by approximately 60%.
- The effect of mobocertinib on the PK of a CYP2C8 substrate is minimal.
- The PBPK analysis is adequate to evaluate the effect of mobocertinib on the PK of a P-gp substrate. The effect of mobocertinib on a P-gp substrate is predicted to be low.

(b) (4)

18.4 Additional Safety Analyses Conducted by FDA

Not applicable.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Nonclinical Reviewer	Kelie Reece, PhD	CDER/OOD/DHOT	Sections: 5	**Select one:** X Authored X Approved
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Nonclinical Team Leader	Emily Wearne, PhD	CDER/OOD/DHOT	Sections: 5	**Select one:** X Authored X Approved
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Nonclinical Team Division Director N/A (NME only)	John K. Leighton, PhD	CDER/OOD/DHOT	Sections: 5	**Select one:** ___ Authored X Approved
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Clinical Pharmacology Reviewer	Kimberly Maxfield, PhD	CDER/OTS/OCP/DCP II	Sections: 6 and 18	**Select one:** x Authored ___ Approved
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Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	CDER/OTS/OCP/DCP II	Sections: 6 and 18	**Select one:** x Authored x Approved
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Division of Pharmacometrics (DPM)	Xinyuan Zhang, PhD	CDER/OTS/OCP/DPM	Sections: 6 and 18.3	**Select one:** X Authored ___ Approved

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Division of Pharmacometrics PBPK Team Leader	Yuching Yang, PhD	CDER/OTS/OCP/DPM	Sections: 6 and 18.3	**Select one:** ___ Authored X__ Approved
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Division of Pharmacometrics (DPM) Reviewer	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections: 6 and 18.3	**Select One:** __X_ Authored ____Approved
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Division of Pharmacometrics (DPM) Team Leader	Jiang Liu, PhD	CDER/OTS/OCP/DPM	Sections: 6 and 18.3	**Select One:** ____Authored _X__ Approved
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Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCP II	Sections: 6, 12, 18.3	**Select one:** ____Authored x__ Approved
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Clinical Reviewer	Elizabeth Duke, MD	CDER/OOD/DO2	Sections: 8	**Select one:** X__ Authored X__ Approved
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Clinical Reviewer	Liza Stapleford, MD	CDER/OOD/DO2	Sections: All	**Select one:** X__ Authored X__ Approved
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Clinical Team Leader	Nicole Drezner, MD	CDER/OOD/DO2	Sections: All	**Select one:** x Authored x Approved
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Statistical Reviewer	Anup Amatya, PhD	CDER/OTS/DBV	Sections: 8.1,8.3	**Select one:** x Authored ___ Approved
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Statistical Team Leader	Pallavi Mishra-Kalyani, PhD	CDER/OTS/DBV	Sections: 8	**Select one:** X Authored X Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001675542, cn=Pallavi S. Mishra-kalyani -S Date: 2021.09.11 08:33:21 -04'00'			
Deputy Division Director (OB)	Yuan-Li Shen, Dr. P.H.	CDER/OTS/DBV	Sections: 8	**Select one:** X Authored X Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling (ADL)	Barbara Scepura	CDER/OOD	Sections: All	**Select one:** X___ Authored ____ Approved
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Cross-Disciplinary Team Leader (CDTL)	Nicole Drezner, MD	CDER/OOD/DO2	Sections: All	**Select one:** _X_ Authored _X_ Approved
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Deputy Division Director (Clinical)	Martha Donoghue, MD	CDER/OOD/DO2	Sections: All	**Select one:** X___Authored _X_ Approved
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