EMA/787858/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Exkivity

International non-proprietary name: mobocertinib

Procedure No. EMEA/H/C/005621/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AECI	adverse event of clinical interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC∞	area under the plasma concentration-time curve from time 0 to infinity
AUC24	area under the plasma concentration-time curve from time 0 to 24 hours
BCRP	breast cancer resistance protein
BTD	Breakthrough Therapy Designation
CHMP	Committee for Medical Products for Human Use
Cmax	maximum observed plasma concentration
CMC	chemistry, manufacturing, and controls
cORR	confirmed objective response rate
CR	complete response
CSR	clinical study report
DCR	disease control rate
DDI	drug-drug interaction
DiC	drug-in-capsule
DiC-A	drug-in-capsule by Process A
DiC-B	drug-in-capsule by Process B
DiC-C	drug-in-capsule by Process C
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EHR	electronic health record
EMA	European Medicines Agency

EMR	electronic medical record
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FIH	first in human
GI	gastrointestinal
HER2	human epidermal growth factor receptor-2
IA	interim analysis
ILD	interstitial lung disease
iORR	intracranial objective response rate
IRC	independent review committee
ISS	integrated summary of safety
L858R	Leu858Arg
MAA	Marketing Authorisation Application
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NSCLC	non–small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PBPK	physiologically based pharmacokinetic
PD-(L)1	programmed cell death protein 1 or programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PT	Preferred Term

QD	once daily
QOL	quality of life
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
RECIST	Response Evaluation Criteria in Solid Tumors
rhCYP	recombinant human cytochrome P450 enzyme
RP2D	recommended phase 2 dose
RWD	real-world data
SAE	serious adverse event
SAWG	Scientific Advice Working Party
SOC	System Organ Class
SD	stable disease
Study 101	Study AP32788-15-101
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
Tmax	time of first occurrence of Cmax
TN	Treatment-Naïve
ULN	upper limit of normal
US	United States
WT	wild type

1. CHMP Recommendation

Based on the review of the data on quality, safety, efficacy, the application for Exkivity (mobocertinib) in the treatment of

> "*Exkivity as monotherapy is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive advanced non-small cell lung cancer (NSCLC), who have received prior platinum-based therapy*"

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (redacted from published report).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions (redacted from published report).

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

(i) benefit in the intended target population is not sufficiently justified

(ii) CMA criteria are not fulfilled

The Application for conditional but not full marketing authorisation is deemed appropriate due to the non-comprehensiveness of clinical data.

1.1. Questions to be posed to additional experts

The CHMP considers the SAG Oncology should be consulted with regard to the relevance of the mobocertinib data to support an indication for the "treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive advanced non-small cell lung cancer (NSCLC), who have received prior platinum-based therapy".

1.2. Inspection issues

1.2.1. GMP inspection(s)

A request for GMP inspection is not required.

1.2.2. GCP inspection(s)

One GCP site inspection has been performed by the FDA at the University of California San Diego (Moores Cancer Center, La Jolla, California, USA) in May 2021. Nine subjects from the inspected site were included into study 101 part 2, two of these 9 subjects are part of the post-hoc defined 'pooled prior platinum analysis set'. No significant observations are reported (no FDA Form 483 was issued).

During the assessment, no relevant concerns were identified about the compliance with GCP or related regulatory and ethical standards that may change the overall conclusion. Thus, no request for a GCP inspection is considered necessary.

1.3. New active substance status

Based on the review of the data, it is considered that the active substance mobocertinib contained in the medicinal product Exkivity is qualified as a new active substance.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The initially claimed therapeutic indication was: "*Exkivity as monotherapy is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received prior platinum-based chemotherapy*".

The claimed indication was changed during the procedure to: "*Exkivity as monotherapy is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive advanced non-small cell lung cancer (NSCLC), who have received prior platinum-based therapy*".

2.1.2. Epidemiology (based on applicant's dossier)

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. Globally, in 2018, there were more than 2 million new cases of lung cancer and 1.8 million lung cancer–related deaths [Sung H et al, 2021]. Incidence rates are similar on a per capita basis across major countries and regions. In Europe, there were an estimated 470,000 cases of lung cancer diagnosed in 2018 across 40 countries, with 388,000 deaths [Ferlay et al 2018].

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 [Molina et al 2008; O'Kane et al 2017; Herbst et al 2018]. 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% [O'Kane et al 2017; Ellis et al 2011].

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 [Graham et al 2018; Han et al 2015; Kohno et al 2015; Kris et al 2014; Yatabe et al 2015]. Incidence of this driver alteration is more prevalent in East Asia, affecting 50% to 60% of patients with NSCLC adenocarcinoma [Shi et al 2014]. 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 US, respectively [Midha et al 2015]. 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 [Yasuda et al 2012; Arcila et al 2013; Fang et al 2019]. 4% to 12% 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 [Yasuda et al 2012; Arcila et al 2013; Fang et al 2019; Oxnard et al 2013; Riess et al 2018]. Clinical data for exon 20 insertion mutations is limited.

2.1.3. Biologic features (based on applicant's dossier)

Unlike common EGFR mutants, EGFR exon 20 insertion/duplication mutations are typically insensitive to 1st-/2nd-generation EGFR TKIs. The mechanism underlying this insensitivity has not been definitively characterized but is most likely influenced by the indirect impact of these mutations, located distally to

the adenosine triphosphate (ATP) binding pocket, on the active site [Eck et al 2010]. EGFR exon 20 insertion mutations, like the common mutations (exon 19 deletions and L858R), reduce the enzyme's affinity for ATP. However, unlike the common mutations, EGFR exon 20 insertion mutations (as exemplified by the NPG insertion mutant [D770_N771insNPG]) do not directly alter the structure of the active site. Instead, these mutations 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 [Yasuda et al 2013]. It is predicted that this altered conformation distal to the ATP binding pocket prohibits the efficient binding of the 1st-/2nd-generation TKIs in EGFR exon 20 insertion mutations. In rare cases (<5%), when the insertion occurs inside the C-helix of the EGFR kinase domain, as exemplified by the A763_Y764insFQEA insertion, the sensitivity to existing TKIs has been observed [Burnett et al 2021].

2.1.4. Clinical presentation, diagnosis

The majority of patients with lung cancer have advanced disease at clinical presentation. This may reflect the aggressive biology of the disease and the frequent absence of symptoms until locally advanced or metastatic disease is present. High-risk patients may be diagnosed while asymptomatic through screening with low-dose computed tomography.

Symptoms may result from local effects of the tumour, from regional or distant spread, or from distant effects not related to metastases (paraneoplastic syndromes, e.g. SIADH, Cushing). Approximately three-fourths of non-screened patients have one or more symptoms at the time of diagnosis. One study noted that the most common symptoms at presentation were cough (55 percent), dyspnea (45 percent), pain (38 percent), and weight loss (36 percent) [Kocher F et al, 2015]. Haemoptysis also belongs to the most common clinical manifestations at presentation.

Every patient with suspected NSCLC should undergo computed tomography (CT) scan of the chest and upper abdomen (usually contrast-enhanced) to evaluate the extent of the primary tumour and potential spread to the mediastinum, liver, and adrenal glands. Radiographic staging does not obviate the need for tissue biopsy. A diagnosis of NSCLC is made based upon the pathologic evaluation of cytologic (e.g. pleural fluid) or histopathologic (e.g. tissue biopsy) specimens. The initial radiographic staging optimises the selection of a biopsy site and preferred modality to obtain a pathologic sample. Consideration should be given to obtaining a large enough sample to allow supplemental immunohistochemical and genetic analysis. Adenocarcinoma, squamous carcinoma, adenosquamous carcinoma, and large cell carcinoma are the four major histological subtypes of NSCLC. The main entity on the differential diagnosis of NSCLC is small cell lung cancer (SCLC). While clinical and imaging features can help the clinician distinguish NSCLC from SCLC, pathologic review of adequate biopsy specimens is required to make this distinction. [UpToDate®, 2021].

2.1.5. Management

With the exception of those patients found to have low frequency insertion mutations, such as A763_Y764insFQEA, most patients with NSCLC harbouring EGFR exon 20 insertion mutations (~95%) are usually resistant to first and second-generation EGFR TKIs erlotinib, gefitinib, afatinib, or dacomitinib (NCCN guideline, NSCLC, Version 6.2021). The third generation EGFR TKI osimertinib has also been evaluated in a small single-arm trial in patients with NSCLC with EGFR exon 20 insertion mutations, and showed some interesting activity [Veggel et al 2020, Piotrowska et al 2020].

However, patients with metastatic NSCLC (adenocarcinoma) harbouring EGFR exon 20 insertion mutations are usually treated as patients without a driver mutation. Initial treatment usually consists of carboplatin or cisplatin in combination with pemetrexed with or without an immune checkpoint (PD-1/PD-L1) inhibitor. Subsequent therapy options include systemic immune checkpoint inhibitor

monotherapy (if no previous IO) or (independent of previous IO) monotherapy with docetaxel, pemetrexed, gemcitabine or combination therapy with ramucirumab/docetaxel (NCCN 6.2021 - NSCLC).

Lately, amivantamab, a bispecific EGFR-mesenchymal epithelial transition (MET) antibody and mobocertinib received accelerated approval in the USA for the patient population discussed in this MAA in May and September 2021, respectively. In the EU amivantamab received a CMA in December 2021. Its role in treatment is to be clarified.

2.2. About the product

Exkivity (mobocertinib) is an orally available kinase inhibitor of the EGFR that irreversibly binds to EGFR exon 20 insertion mutations at lower concentrations than wild type (WT)-EGFR leading to the inhibition of the receptor activity.

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: not yet assigned

The recommended dose is 160 mg once daily. Treatment should be continued until disease progression or is no longer tolerated by the patient.

2.3. The development programme/compliance with guidance/scientific advice

CHMP scientific advice

With regard to the quality, preclinical, clinical pharmacology and clinical development program of mobocertinib for NSCLC patients harbouring exon 20 insertion mutations the applicant received CHMP feedback by 5 scientific advice procedures concerning this MAA:

- EMEA/H/SA/3828/1/2018/III: In June 2018 CHMP advice was given on the now pivotal single-arm study AP32788-15-101 (main messages see below) and on the non-clinical and the clinical pharmacology development program.
- EMEA/H/SA/3828/1/FU/1/2019/II: In April 2019 CHMP advice was given on the 1st-line RCT TAK-788-3001, now proposed for the provision of comprehensive data as key SOB in a CMA (main messages see below).
- EMEA/H/SA/3828/2/2020/I + EMA/SA/0000051782: In 2020 and 2021 CHMP advice was given with regard to the quality development.

Regarding the pivotal single-arm trial AP32788-15-101 the main messages from CHMP in 2018 were (EMEA/H/SA/3828/1/2018/III):

- "Independent registrational studies in treatment-naïve and pre-treated patients are highly recommended" and
- "…, it is unlikely that data reported from the proposed uncontrolled extension cohort would be considered sufficient to support an approval. The benefit of TAK-788 will need to be judged on the basis of an expected confirmed ORR with a lower bound of the 95% CI above 25% [for further details on the expected response rates in the treatment-naïve (TN), the relapsed/refractory (R/R) and the pooled setting see table below taken from slide 23 of the applicant's presentation for the discussion meeting],

	TN	R/R	Pooled
True rate, %	50	35	40
Uninteresting rate, %	35	20	25
Sample size	30	90	120
Power, %	N/A	86.6	>90

which may indeed not be considered sufficiently outstanding to justify submitting an application for conditional approval (provided all the other requirements are fulfilled). As stated above, only exceptional ORR and DoR could suffice to conclude clinically relevant benefit in the absence of a comparator, and to demonstrate a major therapeutic advantage over current therapeutic alternatives."

Of note, the applicant followed this advice with regard to the separation of the first-line and the second-/later-line population in the further clinical development. However, the uncontrolled extension cohort was performed despite CHMP advice with the aim to provide pivotal evidence for the second-/later-line population and is now provided as pivotal evidence in this MAA.

Regarding RCT TAK-788-3001 the main messages from CHMP in April 2019 were (EMEA/H/SA/3828/1/FU/1/2019/II):

- Patients in the control arm should be treated as patients with no oncogenic drivers.
- "Platinum doublet chemotherapy as comparator could be acceptable from a regulatory perspective."
- PFS was accepted as primary endpoint, a detrimental effect on OS should be excluded. Therefore, one-way cross-over was not endorsed (see below IA).
- Proposed interim analysis (IA) for efficacy after 159 PFS events (study fully recruited with 318 patients) was not supported:
  Response to question 3: "According to Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5), only in case of a large effect on PFS and/or a clearly favourable safety profile a precise estimate of OS may not be needed for approval. In consequence, the proposed design with a systematic one-way crossover of patients from the reference arm to the experimental treatment arm is not endorsed. Therefore, the proposed PFS interim analysis, with early stopping for efficacy based on very few OS events observed, is not endorsed. In the case of an early stop for efficacy, one-way cross-over would be systematic and unavoidable, and the subsequent comparison in OS, deemed very important, would be surely hampered. Further, it is noted that according to the proposed adaptive design, with an event-size reassessment the minimum detectable statistically significant HR at the final PFS analysis would be 0.788, corresponding approximately to a 1.75-month improvement. Such an improvement cannot be defined as a large effect on PFS, and therefore a precise estimate of OS in order to exclude a detrimental effect will be required, which is in contrast with the proposal to allow one-way cross-over. For further methodological considerations on the proposed interim analysis, please refer to the response to question 5."
  Response to question 5: "… Concerns of insufficient data maturity" were raised. "Generally, robust evidence for a clinically relevant effect of TAK-788 will be required, which should not be reduced to the question of a statistically significant effect on PFS at interim. Firstly, it seems unlikely that the time horizon of PFS will be adequately covered after observation of PFS events in 50% of patients, in particular hampering the evaluation of long-term PFS effects. Secondly, evaluation of OS data at interim based on expected 93 deaths at interim (29%), will probably not be conclusive with regard to the question whether a detrimental effect on OS can be reasonably excluded. If cross-over after progression is allowed (please refer to answer to question 3), OS data at interim will be even less conclusive. After declaring the study successful at interim, allowing cross-over may be unavoidable (and may also include patients

prior to progression) such that OS data may well be inconclusive even if patients are continued to be followed for OS after final PFS analysis. Furthermore, assessment of consistency in important subgroups may be prevented by insufficient event numbers in subgroups".

- Regarding the question whether studies 'TAK-788-3001' and 'AP32788-15-101' could be sufficient for line-independent MA it was stated that "provided that the proposed pivotal phase 3 study in first-line treatment … provides convincing and robust evidence for the efficacy and safety of TAK-788 in the first-line setting the proposed data package might allow for a wider indication wording."

Of note, as to the study protocol provided for the now ongoing study TAK-788-3001 (Amendment No 6; date 22 Jan 2021) the interim analysis for PFS and one-way cross-over – as discussed and not supported in the scientific advice 2019 (EMEA/H/SA/3828/1/FU/1/2019/II) – is still performed in that way.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Suitable Qualified Person declaration has been provided by the batch release site to confirm EU GMP compliance of the API manufacturers for mobocertinib for the current synthesis.

Satisfactory manufacturing authorisations has been provided for the drug product manufacturing sites involved in the procedure.

GLP

All pivotal toxicology studies were conducted in accordance with GLP regulation.

GCP

The applicant states that all clinical trials discussed in this MAA meet the ethical requirements of Directive 2001/20/EC and were performed in compliance with the ICH-GCP including clinical trials conducted outside the European Union.

GCP inspection is to be discussed (see above section 1.2.2).

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

This application concerns a centralised procedure under 'mandatory scope' [Article 3(1) of Regulation (EC) No 726/2004; Annex (3) - New active substance for mandatory indications].

2.5.2. Conditional marketing authorisation

Regulation (EC) No. 507/2006 identifies conditions under which a product falls within the scope for requesting a CMA and stipulates the requirements necessary to fulfil a CMA. Those products for which a CMA may be requested must fall within 1 of the following 3 categories: 1. Used to treat seriously debilitating or life-threatening diseases, 2. Used in emergency situations, 3. Is an orphan medicinal product.

It is considered established that the sought indication in locally advanced or metastatic non-small cell lung cancer (NSCLC) falls within the first category.

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

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

  Applicant's claim: The ongoing randomised controlled open-label phase 3 study TAK-788-3001 comparing mobocertinib monotherapy versus a pemetrexed-platinum–based chemotherapy in patients with treatment-naïve (i.e. 1st-line setting) NSCLC with EGFR exon 20 insertion mutations should be used to fulfil specific obligations associated with a conditional marketing authorization.
- Unmet medical needs will be addressed

  Applicant's claim: Patients with EGFR exon 20 insertion mutation-positive locally advanced or metastatic NSCLC are commonly treated like NSCLC patients with no driver mutations. The currently available therapies (EGFR TKIs, chemotherapy, and immunotherapy) have limited clinical benefit to patients with *EGFR* exon 20 insertion mutation-positive advanced NSCLC after at least 1 prior therapy. There are also concerns about adverse drug reactions (ADRs). Furthermore, many of the available chemotherapy and immunotherapy agents also have the inconvenience of an intravenous route of administration, requiring patients to travel to a clinic/hospital for the treatment and requiring the healthcare facilities to have appropriate resources and trained healthcare providers.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required

  Applicant's claim: 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.

  Metastatic NSCLC is incurable; thus, treatment aims to delay disease progression for as long as possible, prolong survival as much as possible, and reduce tumour-related symptoms and maintain, if not improve, the patient's QOL. Treatment decisions are complex and involve a fine balance weighing potential benefits against possible risk with patient preferences often differing from expert judgement.

  Mobocertinib offers an oral and convenient therapeutic option for patients. Compared with other therapeutic options that are given by an intravenous route of administration, daily oral self-administration of mobocertinib poses no additional burden to patients and caregivers in terms of hospital or clinic visits and other healthcare resource utilization. Moreover, it provides improved clinical benefits to patients compared to currently available therapies.

2.5.3. New active substance status

Based on the review of available data on the active substance, the CHMP consider that mobocertinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

2.5.4. Orphan designation

Not Applicable

2.5.5. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0161/2020 on the granting of a (product-specific) waiver.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The subject of this centralised application is the drug product Exkivity, containing Mobocertinib succinate as the active substance.

Full information on the active substance Mobocertinib succinate is provided in Module 3.2.S. There is no reference to an ASMF. A new active substance status is claimed in the EU.

Full information on the drug substance Mobocertinib succinate is provided in Module 3.2.S. The drug substance is a mono succinate salt.

Mobocertinib drug product is currently formulated as hard capsules (40 mg). Other ingredients are gelatin and titanium dioxide.

The hard capsules are packed in PCTFE/PVC blister sealed with aluminium foil; 40 mg hard capsules cartons 112 hard capsules.

3.1.2. Active Substance

3.1.2.1. General Information

Nomenclature and structure have been satisfactorily described and relevant physical-chemical properties have been sufficiently presented.

3.1.2.2. Manufacture, process controls and characterisation

GMP compliance for the current manufacturing sites are demonstrated.

The current manufacturing process was used to manufacture the drug substance used in Phase 2/3 clinical trials.

The manufacturing process is sufficiently described, including equipment used, all process parameter like processing times, and IPCs used.

The definition of the starting material is acceptable. Information about starting material are sufficient. The SMs have been sufficiently characterized by different spectroscopic and chromatographic methods. Synthesis schemes of the manufacturing of SMs used been presented in S.2.3 including information about the solvents and reagents used.

The other materials are sufficiently specified. Only the methods used for controlling the other materials could not be located.

No starting materials or raw materials of human or animal origin are used in the drug substance manufacturing process.

Information about critical process parameters and the corresponding process steps is sufficient in conjunction with S.2.6, Manufacturing process development.

For each isolated intermediate, information has been provided on specification and description of analytical methods used. The possible impurities of the manufacturing process has been listed and their fate throughout the process, and the potential for the purge of these process impurities in the isolation and purification of the process intermediates and the final drug substance have been exanimated.

Mobocertinib succinate is not a sterile drug substance and is not manufactured by aseptic processing. Therefore, drug substance process validation and or evaluation data is not required to be included.

The process development has been sufficiently described. Three, basically comparable synthetic routes have beenused and their changes made have been described sufficiently. Batch history for the use of Mobocertinib succinate drug substance is sufficiently described. The AS batches used is non-clinical and clinical trials are comparable The differences are well described.

Quality attributes of Mobocertinib succinate were evaluated; the impact of Mobocertinib succinate process steps on Mobocertinib succinate quality attributes has been discussed; the quality attributes are impacted by multiple stages in the DS manufacturing process.

Process characterization studies were performed to establish appropriate normal operating and proven acceptable ranges. These studies used multivariate design of experiments (DOE) and Univariant Stability Studies, to support the definition of process parameter criticality. The resulting PARs, NORs, and target values (set points) are listed.

The molecular and physico-chemical structure of Mobocertinib succinate has been investigated by NMR, UV, FT-IR, mass, element analysis, single crystal X-Ray and chirality. Furthermore, the drug substance is physically characterized regarding melting/decomposition temperature, particle size, hygroscopicity, solubility, polymorphism, and solid state stability. The drug substance has been sufficiently characterised.

The related impurity discussion is very short but acceptable. There are six impurities controlled in the AS, none of them specified at levels above the ICH Q3A identification limits. Inorganic impurities are sufficiently specified. The discussion about residual solvents is also very short but acceptable.

The guideline ICHM7 does not apply to drug substances and drug products intended for advanced cancer indications, the discussion about genotoxic impurities is acceptable.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The drug substance specification is mostly set on general requirements of Ph. Eur. and on the batch results obtained.

All non-compendial methods used are described in detail. The applied methods are in accordance with current technical and scientific requirements.

The validation data provided for the methods used are in accordance with the requirements of the relevant ICH guidelines.

The batch results presented show the high purity of the drug substance manufactured by all three manufacturing processes used during the development of the drug product.

Batch analysis results confirm batch-to-batch consistency and support the drug substance specification.

Sufficient reference standard for Mobocertinib succinate are used.

The container closure system is sufficiently described.

3.1.2.4. Stability

Stability studies of three Mobocertinib succinate primary stability batches and four supportive stability batches have been performed in line with ICH Q 1A (R2) guideline. Six stability batches of Mobocertinib succinate were manufactured by the proposed commercial process, one batch by an earlier process; all of the batches are packed in the commercial packaging.

By now, up to 36 months data are available for real time conditions and intermediate conditions, and six months data for accelerated conditions. The data from the primary and supportive stability studies show the same trends over time at the long-term and accelerated conditions, in that no significant change occurs over time for any of the attributes.

Sufficient forced stability studies were conducted which show the stability indicating nature of the method used.

Based on the presented stability data, the re-test period proposed by the applicant is acceptable if stored in container closure system

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

The composition of the drug product, Mobocertinib 40 mg capsule, is satisfactorily described. Common excipient and components are used.

Properties of the drug substance, which are relevant for the drug product manufacture, have been sufficiently explained.

The only excipient used is a hard gelatin capsule shell with a black imprint. The gelatin capsule shell is a standard and is commonly used in the pharmaceutical industry.

Compatibility of the drug substance with the imprinted hard gelatin capsule was demonstrated through clinical and ongoing stability studies.

Mobocertinib drug product has been developed as an immediate release (IR) formulation without any other excipients than the capsule and has remained essentially unchanged over the course of development.

Critical quality attributes (CQAs) of the drug product were identified for Mobocertinib capsules and are monitored by IPCs as well as release and stability test and specifications throughout product development.

The formulation variables did not have any impact on the drug product quality. The formulation is adequate for commercial formulation of Mobocertinib. No overages are used in the formulation of the Mobocertinib capsules.

Mobocertinib is a highly soluble compound with high permeability; therefore, it exhibits the characteristics of a BCS Class 1 compound. Mobocertinib capsules are classified as a rapidly dissolving DP from pH 1.2 to 6.5 under USP Apparatus I conditions at 100 rpm and also rapidly dissolved at pH 1.2 under USP Apparatus II conditions at 50 rpm (final QC method).

The drug product CQAs and manufacturing process were assessed to determine CPPs requiring control.

To ensure manufacturing consistency and product quality with respect to the drug product CQAs, material and process controls were established. The major controls in place are grouped into six categories: in-process control (written in the batch record), good manufacturing practice (GMP) procedure (controlled by site standard operating procedures), incoming material specification, environmental control in the manufacturing suite, process understanding (e.g., acceptable ranges determined from development studies), and drug product specification. A detailed control strategy has been provided.

The primary container closure system for Mobocertinib capsules drug product is a blister pack consisting of PCTFE/PVC film and peel-off aluminum lidding foil. The blisters are placed in a carton box as a secondary container.

Information provided for microbial testing is acceptable.

3.1.3.2. Manufacture of the product and process controls

The manufacturers are also named in module 1. Sufficient GMP and QP declarations are presented.

The batch formulas provided are in accordance with the composition documented in P.1. The manufacturing process and the stability performance of the formulation do not require the use of an overage.

The manufacturing process consists of six steps and is controlled by IPCs and is described in detail. The flow diagram of the manufacturing process has been provided including the IPCs conducted.

Validation Master Plan, Process Validation Controls and Acceptance Criteria have been presented for Mobocertinib capsules. The process validation protocol specifies the process to be run at fixed environmental conditions. The same environmental conditions are also be specified in the process description.

There are only compendial excipients used in the manufacturing of Mobocertinib capsules. The only animal-derived material used in the manufacture of Mobocertinib capsules is the gelatin in the capsule shells. The gelatin used in the capsule shells is derived from 100% bovine sources and is acceptable for use by TSE-CEPs. The components of the black printing ink used for the imprint on the capsule shell are from synthetic sources except for shellac. Shellac is derived from the lac insect. CoAs have been provided. No novel excipients are used for the manufacture of Mobocertinib capsules.

3.1.3.3. Product specification, analytical procedures, batch analysis

The release and stability specifications presented cover relevant parameters for this intermediate form and are suitable to control the quality of the drug product with exception of the shelf-life assay specification.

Pharmacopoeial methods are not described in detail, only a reference to the pharmacopoeia is provided.

The method used for identification, assay and impurities are identical with the corresponding drug substance method, the method for the drug product is also suitable.

The non-compendial methods for the test parameters have been described in detail including the principle of the method, the equipment parameters, the sample and standard preparation, the calculation formula, and a System Suitability Test. The SSTs used are suitable to control the methods during their performance. The applied methods are in accordance with current technical and scientific requirements.

The validation data provided are in accordance with the requirements of the relevant ICH guidelines.

Satisfactory batch analyses have been presented. The batch analyses data confirm consistency and uniformity of the product based on the parameters tested and indicate the reproducibility of the manufacturing process for the drug product.

A risk assessment on elemental impurities in accordance with principles outlined in ICH Q3D has been performed for the drug substance, only, including results of the potential elemental impurities. The results of batches tested show that none elemental impurities could be found above the control threshold defined as 30% of the PDE as defined in ICH Q3D.

The applicant declares that the Risk of introduction of elemental impurities to the drug product from excipients (capsules), manufacturing, and container closure is considered low. In addition, elemental impurities are well controlled under the commercial drug substance manufacturing process. As such, elemental impurities are not adopted in the commercial drug product specification.

A report on nitrosamine risk assessment has been presented. The outcome is that the drug product represents no risk.

The applied primary packaging systems are standard for solid oral formulations. The sufficient specification for the primary packaging materials (foil) includes specifications of the plastic materials (Heat seal layer) for identity, and impurity (specified according Ph. Eur).

3.1.3.4. Stability of the product

The conditions used in the stability studies are according to the ICH stability guideline. The drug product control tests and specifications are set adequately.

Until now, 12 months-data at 5°C, at 25°C, at 30°C and at 40°C are available of three primary lots and six months at the accelerated condition. These primary lots are representative of the commercial drug product manufacturing process. A supportive development stability study was completed for one lot packaged in the container closure system similar to the packaging intended for commercial packaging: PCTFE/PVC with a peel off aluminium lidding foil and demonstrated that the drug product is stable up to 6 months when stored at 30°C/75% RH and 40°C/75% RH. An extrapolation to 24 months is acceptable.

The only difference between the primary stability and the commercial blister packaging is the push through versus the peel off lidding, respectively.

Stability studies are ongoing for one lot of Mobocertinib capsules in the bulk packaging configuration.

Data from the stress stability studies, data from the freeze/thaw study and data from the heat cycling study demonstrate that Mobocertinib are stable

Photo-stability results indicate that Mobocertinib capsules are not light sensitive and therefore no precautionary packaging or labeling is required.

The data from the primary and development stability studies show the same trends over time at the long-term and accelerated storage conditions, in that no significant change occurs over time for any of the attributes.

The recommended storage condition is "This medicinal product does not require any special temperature storage conditions in accordance with Guideline on Declaration of Storage Conditions (CPMP/QWP/609-96 rev 2, November 2007)."

Based on the review of the data on quality, at D180 all outstanding issues were resolved or the responses were accepted. From the quality point of view, positive benefit risk assessment can be stated. The application is approvable with commitments on the Quality part.

3.2. Non-clinical aspects

3.2.1. Introduction

The proposed indication for Exkivity is a monotherapy treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation–positive locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received prior platinum-based chemotherapy. The active substance in the medicinal product is mobocertinib (also known as TAK-788 and AP32788).

EGFR (also known as ErbB1) belongs to the ErbB family of receptor tyrosine kinases, which also includes human epidermal growth factor receptor 2 (HER2, ErbB2), HER3 (ErbB3), and HER4 (ErbB4). Genetic alterations in *EGFR* or *HER2* can lead to aberrant activation of EGFR or HER2 proteins, resulting in increased stimulation of downstream signalling pathways (such as RAS/RAF/MEK/ERK and PI3K/AKT/mTOR) and dysregulation of DNA synthesis and cell proliferation.

The available tyrosine kinase inhibitors (TKIs) targeting EGFR and HER2, which are approved for treatment of NSCLC include the "first-generation" EGFR TKIs erlotinib, gefitinib, and icotinib, the "second-generation" TKIs afatinib and dacomitinib, and the "third-generation" TKI osimertinib. They vary in their ability to inhibit specific genetically altered (mutant) variants of EGFR and HER2, with effective inhibition of some variants requiring a higher level of TKI exposure than can be tolerated by patients. In particular, there are no approved therapies for NSCLC with EGFR exon 20 insertion mutations, and other therapeutic options provide limited benefit.

Mobocertinib was designed to have a strong potency against EGFR exon 20 insertion mutants while having lower activity on wild-type (WT) EGFR. It also inhibits other EGFR mutant variants such as the most common de novo *EGFR* mutations (in-frame deletions in exon 19 and the L858R substitution in exon 21) and the primary treatment-emergent resistance mutation T790M. Mobocertinib is claimed to inhibit these mutants with greater potency than WT EGFR, potentially reducing dose-limiting, class-related toxicities (e.g. rash) associated with WT EGFR inhibition.

The non-clinical program has been designed in accordance with the ICH S9, a guideline for non-clinical evaluation of anticancer pharmaceuticals.

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

Mobocertinib covalently binds to wild-type and exon 20 insertion mutant EGFR at Cys797. The drug was specifically designed to target EGFR with exon 20 insertion mutations. The mutant variant has a narrower binding pocket as compared to the wild-type receptor. Due to its flexible structure, mobocertinib fits well into the pocket. In addition, the drug features a flexible isopropyl ester residue that interacts with Thr790. Higher selectivity for the mutant over wild-type EGFR is reflected in the K_d

values (the concentrations producing 50% binding): 12,350 nM for WT EGFR and 215 nM for exon 20 NPG EGFR.

The specificity of mobocertinib was evaluated on a large panel of 490 protein kinases including 118 mutant variants. 15 kinases were inhibited with IC_{50} below 2 nM, including all 14 members of the EGFR family, and BLK. In this assay, the IC_{50} values for WT and mutant EGFR variants were comparable. Six additional kinases (JAK3, TXK, BTK, BTK [E41K], BMX, and ACK1) were inhibited with IC_{50} <20 nM. Mobocertinib metabolites AP32960 and AP32914 exhibited similar activity (IC_{50} values within two-fold difference), with AP32914 being in general more potent than the parent drug and AP32960 being slightly less active. The selectivity of mobocertinib for mutant over wild-type EGFR was also investigated in cellular assays.

Mobocertinib inhibited EGFR phosphorylation in A431 NSCLC cell line featuring WT *EGFR* amplification with IC_{50} of 35 nM. The activity of the drug against the mutant variants was studied in murine Ba/F3 cell lines overexpressing the respective mutants. For the variants containing the common activating mutations (exon 19 deletion and an L858R exon 21 mutation) with or without T790M, the IC_{50} values for the inhibition of cell proliferation were 2.4-18 nM, and for the variants containing exon 20 activating insertions (FQEA, NPG, ASV, NPH, and SVD) the respective IC_{50} values were 4.3-22 nM. The metabolites had similar activity profiles. The applicant concluded that mobocertinib was more potent against mutant variants than against WT EGFR. To further support this conclusion, the applicant has provided a literature report of the study in the Ba/F3 cell system engineered to overexpress either WT-EGFR or mutant EGFR (Vasconcelos et al. 2021). It clearly demonstrates that mobocertinib inhibits the cell viability of Ba/F3 cells dependent on EGFR exon 20 insertion mutants more efficiently (IC_{50} values being between 63 and 203 nM) compared to Ba/F3 cells overexpressing WT-EGFR (IC_{50} = 763 nM). However, cell growth inhibition by mobocertinib in the study by Vasconcelos et al. required 5- to 10-fold higher drug concentrations as compared to study ARP553 where also Ba/F3 cells engineered to overexpress the same exon 20 insertion mutants were used (IC_{50} for mutant EGFR between 12 and 22 nM). The applicant together for the 2 approaches for testing their is requested to explain this discrepancy in the context of the clinical efficacy taking into account the unbound clinical concentration of mobocertinib (**OC**). The activity of mobocertinib against an EGFR exon 20 NPH insertion mutant was studied by evaluating its effect on viability of LU0387 cells, a patient-derived NSCLC cell line expressing such a mutant. This cell line is resistant to cisplatin and represents a suitable model because mobocertinib is intended as second-line treatment after platinum-based chemotherapy. Mobocertinib inhibited proliferation of LU0387 (IC_{50} = 21 nM) with a similar potency as afatinib but being much more active compared to erlotinib and gefitinib (133- and 17-fold, respectively). Mobocertinib inhibited proliferation of NSCLC cell lines with exon 19 deletion, with L858R mutation, and with L858R plus a T790M resistance mutation demonstrating IC_{50} values in low nanomolar range (1.3-9.8 nM).

Mobocertinib also binds to Cys805 of HER2. Therefore, its effect on proliferation of Ba/F3 cell overexpressing HER2 exon 20 mutants was assessed. Mobocertinib exhibited high activity in cells with HER2 harbouring exon 20 insertions (YVMA, GSP, G776>VC), exon 20 point mutation L755S and non-exon 20 point mutations (V659E, G660D, S310F and G309E) with IC_{50} in low nanomolar range (3.2-26 nM). Mobocertinib also decreased survival of *HER2*-amplified human breast cancer cell lines (IC_{50} = 7.7-34 nM) with strong selectivity over breast cancer cell lines without *HER2* amplification.

In a patient-derived xenograft model (LU0387) in severe combined immunodeficient mice using a tumour obtained from a lung cancer patient that expressed an EGFR exon 20 insertion mutant, a dose-dependent statistically significant inhibition ($p<0.0001$) of tumour growth was achieved. Relative to vehicle-treated mice, 10 mg/kg mobocertinib inhibited tumour growth by 56%, and 30 mg/kg even led to tumour regression by 87% relative to the tumour size before treatment. Increased efficacy was associated with higher plasma levels of mobocertinib. Levels of AP32914 were in general 3 to 5-fold

lower, and levels of AP32960 generally 3 to 4-fold higher than those of the parent drug. Substantial inhibition of EGFR signalling (pharmacodynamic effect) was observed in tumours from mice dosed with 30 mg/kg, but not 10 mg/kg mobocertinib.

In a murine xenograft model based on human NSCLC H1975 cell line expressing an EGFR-L858R/T790M double mutant, mobocertinib inhibited tumour growth by 44% and 92% at 3 mg/kg and 10 mg/kg, respectively. At 30 mg/kg, tumour regression by 76% relative to the pre-treatment tumour size was achieved. The observed tumour growth inhibition was statistically significant ($p<0.0001$) and dose-dependent.

In a mouse Ba/F3 xenograft model featuring an exon 20 ASV insertion EGFR mutant, a dose-dependent, statistically significant inhibition ($p<0.0001$) of tumour growth was achieved. Relative to vehicle-treated mice, mobocertinib inhibited tumour growth by 77% at 30 mg/kg dose. At the 50 and 100 mg/kg dose levels, the drug induced tumour regression by 19% and 89%, respectively, relative to the tumour size before treatment. Also in this model, efficacy correlated with plasma levels of mobocertinib. Similarly to other studies, levels of AP32914 were somewhat lower, and levels of AP32960 higher, than those of the parent drug.

Xenograft models featuring HER2 mutants were also investigated. In mice bearing Ba/F3 xenografts that expressed a HER2 exon 20 YVMA insertion, a HER2 V659E, a HER2 S310F or a HER2 exon 20 G776>VC insertion mutant, statistically significant inhibition of tumour growth ($p < 0.001$) was observed. Relative to vehicle-treated mice, mobocertinib inhibited tumour growth by 49 – 60% when treated with 30 mg/kg mobocertinib and by 59 – 83% at 50 mg/kg. At the 100 mg/kg dosing of mice with a HER2 exon 20 YVMA mutant, the drug led to tumour regression by 26% relative to the tumour size before treatment. In the latter model, increased efficacy of mobocertinib was associated with increased plasma levels in animals administered 100 mg/kg versus 50 mg/kg.

Across animal xenograft models, systemic C_{max} levels for mobocertinib associated with inhibition of EGFR driven tumour growth were in the range 11-146 ng/mL (19-256 nM). At higher mobocertinib plasma concentrations (117-336 ng/mL = 205-588 nM) tumour regression was observed. Systemic C_{max} levels for mobocertinib associated with inhibition of HER2-driven tumour growth was 435 ng/mL (761 nM), while tumour regression was seen at a dose resulting in C_{max} of 1601 ng/mL (2802 nM). It is noted that the doses tested in other non-clinical HER2 tumour models were lower, but still induced inhibition of tumour growth (30 vs. 50 mg/kg).

For comparison, the steady-state C_{max} of mobocertinib in plasma at the recommended 160 mg dose to patients was 70.4 ng/mL (equivalent to 120.2 nM). Consequently, it can be questioned whether the clinical exposure is sufficiently high to achieve efficient inhibition of EGFR or HER2 activity and tumour growth driven by signalling from these receptors. Direct extrapolation from animal xenograft models is however challenging and not always appropriate. It is noted that supporting PD endpoints have not been included in clinical trials. This is further discussed in the clinical part of this assessment.

3.2.2.2. Secondary pharmacodynamic studies

Mobocertinib selectivity for exon 20 insertion mutant over wild-type EGFR was expected to reduce dose-limiting toxicities associated with WT EGFR inhibition. Western blot analysis of EGFR phosphorylation in lung tissues of mice treated with similarly efficacious doses of mobocertinib and afatinib revealed sustained pronounced reduction of WT EGFR activity after afatinib treatment in contrast to mobocertinib showing less WT EGFR inhibition, which was even reversible. Western blot is known to be a semi-quantitative method characterised by high variability. Therefore, the applicant has supported the conclusion regarding lower inhibitory potency of mobocertinib towards WT EGFR compared to afatinib by the results of the immunoassay of EGFR phosphorylation in A431 cells.

Although A431 are epidermoid carcinoma cells and lung tissues of healthy animals (thus, much more suitable than cancer cells for addressing the safety profile) were analysed only with Western Blot, the conclusion is generally agreed.

In vitro screening of mobocertinib activity in mutant NSCLC cell lines with KRAS and BRAF mutations, MET and PDGF amplifications showed much lower potency as compared to EGFR mutants, with IC_{50} values in micromolar range in all but BRAF mutant cell line (IC_{50} = 63.5 nM). Accordingly, little to no tumour growth inhibition was observed in human lung carcinoma xenograft models with a KRAS Q61K mutation and a MET amplification.

In an off-target activity screening assay, mobocertinib was an antagonist of dopamine receptor D1 (DRD1) and a blocker of the alpha-4 beta-2 nicotinic acetylcholine receptor (nAChR [a4/b2]) at concentrations higher than 5 µM. AP32960 and/or AP32914 were antagonists, inhibitors, or blockers of 7 total targets (DRD1, dopamine receptor D2 [short isoform] [DRD2S], 5-hydroxytryptamine receptor 1B [HTR1B], nAChR [a4/b2], insulin receptor [INSR], lymphocyte-specific protein tyrosine kinase [LCK], and/or norepinephrine transporter [NET]) at concentrations exceeding 1 µM. These concentrations are much higher than the clinically achieved C_{max}. Therefore, these off-target interactions are considered not clinically relevant.

3.2.2.3. Safety pharmacology programme

Mobocertinib, AP32914 and AP32960 inhibited the hERG current with IC_{50} values of 10 µM, 5.1 µM, and 10 µM, which is much higher than the clinical steady-state C_{max} of mobocertinib, AP32960 and AP32914 (120.2, 8.7 and 71.0 nM, respectively). In toxicology studies in rats and dogs (C_{max} up to 118 nM), no drug-related effects on cardiovascular, respiratory or central nervous system were observed. However, mobocertinib induced QT prolongation in humans. The mechanism is unknown, since mobocertinib had no marked effects on hERG channels and on the ECG of dogs. In order to study the torsadogenic potential of mobocertinib, the applicant has agreed to investigate effects of mobocertinib on other cardiac ion channels involved in QT interval prolongation (Cav1.2, KvLQT1/minK and Nav1.5). In addition, the applicant has agreed to assess the potential of mobocertinib to induce early afterdepolarisations (EADs) in a non-GLP-compliant human IPSC-derived cardiomyocyte multi-electrode array (MEA) assay. Both studies will be performed post-marketing. This is acceptable, howerver, the applicant is requested to provide the intended time schedule for these studies (**OC**).

3.2.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted because mobocertinib is intended as monotherapy.

3.2.3. Pharmacokinetics

3.2.3.1. Methods of analysis

The analytical method for mobocertinib determination in aqueous formulations using HPLC with UV detection was developed and validated. The validation parameters were in accordance with the acceptance criteria set, and the latter were in line with the EMA Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**. The LC-MS/MS methods for the analysis of mobocertinib and its active metabolites in rat and dog plasma were developed and successfully validated. The validation parameters were in accordance with the EMA Guideline on bioanalytical method validation. The LC-MS/MS methods for the quantitative determination of mobocertinib dimer in rat and dog plasma were developed. The acceptance criteria for the validation parameters were set markedly wider than specified in the EMA Guideline. However, a critical analysis of the bioanalytical

data on dimer quantification from studies 8002353 (dog) and 8002394 (rat) revealed that the accuracy and precision of the QC samples and the back-calculated standards were largely within the acceptance criteria set by the EMA. Therefore, the validity of the study data is not questioned.

3.2.3.2. Absorption

The absorption of mobocertinib was studied following intravenous and oral administration of mobocertinib as a free base to Sprague-Dawley rats, CD-1 mice and beagle dogs. In addition, absorption of mobocertinib succinate, a clinically relevant form, by intravenous and oral route was investigated in Sprague-Dawley rats and beagle dogs.

Pharmacokinetics of mobocertinib, either as a free base or as a succinate salt (clinically relevant form), after intravenous administration was characterised by high volume of distribution in all species investigated. The systemic clearance was high in rodents and low in non-rodents. Consequently, half-life of the drug was short in mice, moderate in rats and very long in dogs. Following oral dosing of mobocertinib as a free base or as succinate, the drug showed rapid absorption in mice, moderate absorption in rats and moderate to low absorption in dogs. In all species studied, oral bioavailability was moderate, with exception of mobocertinib salt in rats having low bioavailability. Pharmacokinetic profiles were comparable for all three pharmaceutical forms (solution, suspension, capsule).

The potential food effect on mobocertinib dissolution and permeability was investigated using an in vitro dissolution permeation chamber with donor and receiver compartments separated by a biomimetic membrane. Mobocertinib dissolution in the donor chamber was complete at pH 2 and relatively poor (10%) at pH 5. Full dissolution was reached after introduction of either fasted or fed state simulated intestinal fluid. However, 25% less drug was found in the receiver chamber upon fed condition as compared to fasted condition. These results suggest possible slight reduction of mobocertinib oral bioavailability when taken with food.

3.2.3.3. Distribution

Mobocertinib and its active metabolites readily bind plasma proteins. Overall mean percent bound values for the parent drug were similar across species and ranged from 99.3% to 99.5%. For AP32960, the values were comparable and lay between 99.4% and 99.6%. AP32914 exhibited lower degree of protein binding with percent bound values across species ranging from 98.0% to 98.9%. The compounds demonstrated similar affinity for human liver microsomal proteins.

Mobocertinib and AP32960 showed no preferential distribution into red blood cells over plasma in mouse, rat, dog, and human blood, with mean blood-to-plasma ratios similar across species and ranging from 0.95 to 1.42.

Following oral administration of 10 mg/kg [^{14}C]-mobocertinib to Long-Evans rats, radioactivity was widely distributed throughout the tissues as determined by whole-body autoradiography. The site of radiolabelling is acceptable since it is not involved in pharmacological activity. Relatively high tissue concentrations were found in liver, adrenal gland cortex, adrenal gland (entire), kidney outer medulla, small intestine, eye uvea, and thyroid. At the last observation time point, very high radioactivity remained in eye (uvea). Elimination of radioactivity from all tissues was generally very slow. Relatively long half-lives (> 500 h) were observed in eye uvea, non-pigmented skin, adrenal gland (entire), brown adipose, thymus, cardiac blood and adrenal gland cortex. [^{14}C]mobocertinib-related radioactivity appeared to be specifically, but reversibly, associated with melanin. However, the drug showed no phototoxic potential in a GLP-compliant in vitro study with mouse fibroblasts in the presence or absence of ultraviolet radiation (see toxicology section).

No placental and milk transfer studies were conducted.

3.2.3.4. Metabolism

Mobocertinib is extensively metabolised in different species. In microsomes, dealkylation, and oxidation were detected. In hepatocytes, GSH conjugation was observed in addition to the above-mentioned Phase I metabolic pathways. In human hepatocytes, the only metabolite observed was AP32960 (N-demethylated product). It was also the major metabolite in human liver microsomes and in liver microsomes and hepatocytes of the nonclinical species evaluated.

Mobocertinib metabolism is primarily mediated by CYP3A4/5 with minor contribution from CYP2C8, CYP2C9 and CYP2D6. Recombinant human CYP3A4 and CYP3A5 predominantly transformed mobocertinib to AP32960 (> 20%). The active metabolites AP32914 and AP32960 were both further metabolised by CYP-dependent pathways, primarily by CYP3A4 and 3A5.

Using recombinant CYP enzymes, the relative contribution of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 to mobocertinib hepatic clearance was estimated as 0.3%, 1.1%, 2.4%, 1.9%, 0.1%, 0.6%, and 93.5%. Extra-hepatic enzymes CYP1A1 and 2J2 were also involved in the metabolism of mobocertinib.

In vivo metabolism was investigated in rats and dogs. These species were also used in toxicology studies. Metabolic profile proved to be complex. In dog plasma, unchanged drug was the major circulating component, comprising 68.5% of total radioactivity. The plasma metabolites were products of dealkylation and oxidation. The major metabolite in dogs was a cysteine conjugate of mobocertinib accounting for 16.9% of the total dose. Three human circulating metabolites M108, M107, and M106 (products of dealkylation, oxidation and hydrogenation) were observed in dog plasma, urine, faeces, and bile.

Similarly to dog, the parent drug was the most abundant in rat plasma, with 20.48% of plasma radioactivity. Two dealkylation metabolites comprised 10-15% and dealkylation active metabolite AP32960 represented 6.6%. Three mono-oxygenated metabolites accounted together for 9.17% of the total radioactivity. In rat bile, Phase I metabolites were through N-dealkylation, oxidation, and oxidation plus N-dealkylation pathways; each pathway accounted for 3.32%, 3.01%, and 6.79% respectively of the bile total radioactivity. Phase II metabolites, GSH adducts and products of their further biotransformation accounted for 58.89%, hydroxy-glucuronide and dihydroxy-glucuronide accounted for 4.68%. Phase I metabolites in rat urine were formed through N-dealkylation, oxidation, and the combination of both, accounting for 3.57%, 11.53%, and 20.05% of the urinary total radioactivity, respectively. Amide and ester hydrolysis were observed with metabolites at 4.81% and 1.98% of the urinary total radioactivity, respectively. Glutathione conjugates of the Phase I metabolites and derived mercapturic acid pathway products accounted for 23.77%. Glucuronidation metabolites together represented 13.64%. In rat faeces, dealkylation, oxidation and their combination were again the major Phase I metabolic routes, each subgroup accounting for 0.68%, 5.68% and 16.63%, respectively of the faecal total radioactivity. GSH adducts of mobocertinib, of Phase I metabolites, and down-stream metabolites of the GSH conjugates comprised 38.05%.

In humans, five metabolites (dealkylation and oxidation products as well as a cysteine conjugate) were detected in urine and each contributed to less than 0.9% of the dose. In faeces, AP32960 was the most abundant metabolite and represented approximately 12% of the dose. In addition, metabolites derived from oxidation of mobocertinib and a cysteine conjugate were found and ranged from approximately 2% to 6% of the dose. In plasma, mobocertinib itself was the most abundant component and accounted for 7.65% of total extracted circulating radioactivity. Dealkylation product of mobocertinib (M108), cysteine conjugate M70, M107 formed via oxidation and hydrogenation of M108, and M106 formed through N-demethylation of M107, and AP32960 (M67) accounted for 7.14%, 6.76%, 5.94%, 5.30%, and 5.17% of total extracted circulating radioactivity, respectively. There was

no single metabolite accounting for more than 10% of the total extracted circulating radioactivity. Therefore, toxicological evaluation of metabolites is not warranted.

3.2.3.5. Excretion

After oral administration of radiolabelled mobocertinib to normal Sprague-Dawley rats, the vast majority of radioactivity was excreted into faeces. Following oral dosing to bile-duct cannulated rats, biliary excreted radioactivity accounted for 57.8% of total radioactivity indicating that majority of faecal excretion was from biliary elimination. In bile-duct cannulated rats, 37.8% of radioactivity was recovered in faeces. Following oral administration of ^{14}C-mobocertinib to beagle dogs, the radioactivity was predominantly excreted through faeces (40-45% of the dose). In bile-duct cannulated dogs, biliary elimination accounted for 40.3% compared to 18.5% faecal excretion. In both pre-clinical species investigated, renal excretion was minor and accounted for less than 10% of the dose.

3.2.3.6. Pharmacokinetic drug interactions

In vitro studies of CYP enzyme inhibition by mobocertinib, AP32960 and AP32914 identified inhibitory potential of the compounds for CYP2B6, CYP2C8 and CYP3A4/5, with K_i values ranging from 7.6 μM to 18.7 μM. For CYP3A4/5, time-dependent (irreversible) inhibition was observed. For this reason, in vivo evaluation of the DDI potential for CYP3A4/5 is warranted. In vitro data did not suggest possible in vivo relevance for any of the other enzymes studied (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6).

In vitro experiments indicated that mobocertinib and both active metabolites (AP32960 and AP32914) are strong inducers of CYP3A4 warranting in vivo investigations. Mobocertinib moderately induced CYP2C8 and was a weak inducer of CYP2B6 and 2C9. AP32914 weakly induced CYP1A2.

In vitro studies showed that mobocertinib is likely a substrate of P-gp, but not of BCRP, OATP1B1, and OATP1B3. It was not investigated whether mobocertinib is a substrate of MATE1, MATE2-K, OCT1, OCT2, OAT1, and OAT3 but this is acceptable given a low contribution of renal excretion to elimination of mobocertinib. AP32960 is likely to be a substrate of P-gp and possibly of BCRP, and AP32914 is likely a P-gp, but not a BCRP substrate.

Mobocertinib was found to inhibit BCRP, P-gp, and OCT1 in vitro to an extent warranting in vivo studies. The applicant has predicted the effect of mobocertinib on the OCT1 substrate metformin in vivo using PBPK modelling. The PBPK model predicted no effect on metformin exposure but is not considered qualified for the purpose of simulating OCT1-driven DDIs. Based on current knowledge, OCT1 inhibition may impact the metformin response through altered hepatic distribution with little effect on plasma PK. In general, there is a lack of established sensitive OCT1 substrates, and the conduct of an *in vivo* PK study may not be feasible. Still, an effect on OCT1 substrates by mobocertinib cannot be ruled out. Section 5.2 of the SmPC should be updated to reflect that based on in vitro studies, mobocertinib is an inhibitor of OCT1 at clinically relevant concentrations (**OC**).

In addition, both in vitro and in vivo studies revealed mobocertinib potential to induce CYP3A4/5. As CYP3A4/5 induction is mediated by the pregnane X receptor (PXR), CYP2C is co-regulated and P-gp may be also induced. As PXR regulated enzyme interactions other than CYP3A4 has not been studied *in vivo*, the warning in section 4.5 of the SmPC should be retained: "Exkivity may also induce other enzymes and transporters (e.g., CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (e.g., pregnane X receptor activation)." (**OC**).

Furthermore, mobocertinib is an inhibitor of intestinal P-gp and BCRP. No clinical studies have been conducted to evaluate the effect of mobocertinib on substrates of these transporters in vivo, and the

applicant has used PBPK modelling to predict the DDI potential. For the discussion of this issue, refer to Clinical AR / the clinical part of the Overview.

3.2.4. Toxicology

Toxicology studies submitted included repeat-dose toxicity studies in rats and dogs (up to 3 months duration), in vitro and in vivo genotoxicity, reproductive toxicity and phototoxic potential. Additional in vitro genetic toxicity studies were conducted on a number of potential impurities. All pivotal studies were conducted in compliance with GLP regulations and used the intended clinical route of administration (oral).

3.2.4.1. Single dose toxicity

Mobocertinib and both active metabolites were evaluated in single dose toxicity studies in rats and dogs. Within these studies the potential toxicity and TK profile of mobocertinib was evaluated together with the potential reversibility of any findings during a 14-day recovery period.

Single dose administration of mobocertinib was tolerated up to the highest dose tested in rats and dogs. This dose was therefore considered the NOAEL [100 mg/kg (rats) and 10 mg/kg (dogs)]. Prominent target organ was the gastrointestinal tract in both species. Regarding TK there were no differences between male and female animals.

3.2.4.2. Repeat dose toxicity

Non-pivotal 2 weeks repeat dose toxicity studies have been conducted in rats and dogs. The pivotal GLP-compliant repeat-dose toxicity studies of 28-days and 3-months duration have been conducted in rats and dogs. The 28-day studies included an assessment of reversibility 28-days after cessation of dosing and the 3-months studies included an assessment of reversibility 1-month after cessation of dosing at the highest dose level.

Table 3.2.4.2.1 : Non-pivotal repeat-dose toxicity studies with mobocertinib

Species /strain Study ID (GLP)	**Number of animals & gender per group**	**Dose (mg/kg) Route & Duration**	**Noteworthy findings**	**NOAEL / MTD / STD_{10}**
Rat/ Sprague -Dawley ARP524 (**non-GLP**)	5 / sex main study (0-60 mg/kg) 6 / sex satellite TK/ tolerability	0, 10,30, 60, 100, 300 oral for 2 weeks	**10 mg/kg** **30 mg/kg** 1 F died, F:body weight↓,M+ F:ruffled fur, M+F:fur loss, M+F:loose stools, M+F:porphyrin pigment, F:weakness, M:hematuria, M+F:white blood cells↑, F:ALT↑, F:AST↑, F:blood urea nitrogen↑, **60 mg/kg** 2 M died, M+F:body weight↓,M+ F:ruffled fur, M+F:fur loss, M+F:loose stools, M+F:porphyrin pigment, M:weakness, M:hematuria, M+F:white blood cells↑, M:ALT↑, M:AST↑, M:blood urea nitrogen↑, F: liver weight↑	MTD 10 mg/kg
Dog / beagle WIL-69508 (**non-GLP**)	1/sex/group	0, 5, 10, 20, oral for 4 days plus 10-day dose holiday	**5 mg/kg** M:Body weight↓, M+F:food consumption week1↓, week2↑, M:injected sclera eyes, M+F:emesis, M+F:diarrhoea, M: red material in faeces 10 mg/kg M:Body weight↓, M+F:food consumption week1↓, week2↑, M+F:injected sclera eyes, M+F:partial closure eyes, M+F:emesis, M+F:diarrhoea, F: material in faeces **20 mg/kg** M+F:Body weight↓, M+F:food consumption week1↓, week2, M+F:injected sclera eyes, M:partial closure eyes, M+F:emesis, M+F:diarrhoea, M+F: material in faeces, F:reddened gums; F:wet clear material around the mouth	MTD <5 mg/kg
Dog / beagle WIL-69510 (**non-GLP**)	1/sex/group	0, 0.3, 1, 3 oral for 14 days	**0.3 mg/kg** M:Body weight↑, M+F:food consumption ↑, M+F: soft faeces, M+F:diarrhoea, M+F:total protein↓, M+F:albumin↓, M+F:globulin↓, liver weight↑, spleen weight↓, testes weight↓, thymus weight↑ **1 mg/kg** M+F:Body weight↓, M+F:food consumption↓, M+F:soft faeces, M+F:diarrhoea, testis weight↓,liver weight↑, spleen weight↓, testes weight↓, M:thymus weight↑F: ↓ **3 mg/kg** 1 F died, M+F:Body weight↓, M+F:food consumption↓, M+F: soft faeces, M+F: diarrhoea, liver↑, spleen weight↓, testes weight↓, thymus weight↓	MTD 1 mg/kg

The non-pivotal studies in rats and dogs were primarily conducted as exploratory dose range-finding studies.

Target organ toxicity in **rats** included dermal and gastrointestinal systems as well as kidney and liver toxicities. Female rats were more sensitive to mobocertinib compared to male rats, but treatment-related deaths occurred within both gender types. Exposure to mobocertinib and its metabolites AP32960 and AP32914 increased in a mobocertinib dose-related manner with higher values in females compared to male animals (AUC24 was 2.2-fold to 4.6-fold higher). At 10 mg/kg mobocertinib (MTD), the Day 14 C_{max} values were 58.8 and 183 ng/mL and the Day 14 AUC24 values were 690 and 2158 h*ng/mL for males and females, respectively.

Since in the first **dog** study (Study WIL-69508) dosing had to be stopped after 4 days due to poor condition of the animals a follow-up study was performed using significant lower dose levels. In this latter study, one female animal died and this death was attributed to mobocertinib-related gastrointestinal lesions. Gastrointestinal toxicity was most evident, but effects also included changes of liver, thymus, testes and spleen (males only). There was a more than dose-proportional increase in systemic exposure of mobocertinib and the active metabolites. At 1 mg/kg (MTD) C_{max} and AUC values were 67.0 ng/mL and 1010h*ng/mL, respectively.

Table 3.2.4.2.2 : Pivotal repeat-dose toxicity studies with mobocertinib

Species /strain Study ID (GLP)	**Number of animals & gender per group**	**Dose (mg/kg) Route & Duration**	**Noteworthy findings**	**NOAEL / MTD / STD_{10}**
Rat/ Sprague -Dawley WIL-69512 (**GLP**)	20 / sex / group: 10/sex/group to end-of-dosing + 5/sex/group recovery	0, 10, 20, 30, oral for 28 days + recovery of 28 days	**10 mg/kg** Body weight, food consumption↓, hair loss(M+F); salivation (F), RBC↓, WBC↑, albumin↓, globulin↑, fibrinogen↑, lymph nodes enlarged, heart, kidney, pituitary weight↓(M+F); seminal vesicle, prostate gland, liver weight↓(M); thymus, ovary, uterus weight↓ (F) **20 mg/kg** Body weight, food consumption↓(M+F); 1F found dead on day 5 and 1 F on day 19; 1 F was euthanised on day 8 and 3 F on day 17; all other F were dosed up to day 19; M:treated up to day 18 and continued on day 20; salivation, diarrhoea, red urine, hair loss, RBC↓; retic↑ (F), albumin↓, globulin↑, ; enlarged lymph nodes(M+F); heart, kidney, pituitary, thymus, thyroid, epididymides, seminal vesicle, prostate gland weight↓(M); thymus, pituitary, ovary weight↓(F) l **30 mg/kg** Body weight, food consumption↓(M+F); 3 M were euthanized: 1 on day 8 and 2 on day 17; F were euthanised on day 7; M were treated up to day 19; salivation, red urine, hair loss, retic↑, albumin↓, globulin↑; heart, kidney, seminal vesicle/prostate, and thyroid/parathyroid weight↓ **All doses** Pale/blue or cool extremities, cool body, respiration rate↓, unkempt appearance, partial closure of the eyes, rales, dermal atonia, thin body condition, mucoid or soft faeces, diarrhea, brown/red/yellow material on body surface, facial reddening or scrabbing	STD_{10} 10 mg/kg

Rat/ Sprague -Dawley 800235 2 Amend ment 1 (**GLP**)	15 / sex / group: 10/sex/grou p to end-of-dosing + 5/sex/group recovery	Males: 0, 2.5, 5, 10 Females: 0, 1.25, 2.5, 5 oral for 3 months + one month recovery	**Males 0 mg/kg** 2 animals died due to gavage accident (one animal) and hemorrhage of procedural origin (one animal) **Males 2.5** 1 animal died due to deteriorating condition; GI tract: villous atrophy (small intestine), mucosal atrophy (colon and/or cecum), prostate weight↓, mandibular lymph node: hyperplasia, dehydration, nephropathy, globulin↑, albumin↓ **Males 5** 1 animal died accidental, GI tract: villous atrophy (small intestine), mucosal atrophy (colon and/or cecum), prostate weight↓, mandibular lymph node: hyperplasia, dehydration, nephropathy, ALA/AS P↑ **Males 10** GI tract: villous atrophy (small intestine), mucosal atrophy (colon and/or cecum), prostate weight↓↓, thin hair coat, mandibular lymph node: hyperplasia, dehydration, nephropathy, WBC↑, BW↓, Ala/Asp↑, (liver necrosis) **Females 1.25** GI tract: villous atrophy (small intestine), mucosal atrophy (colon and/or cecum), uterus weight↓ **Females 2.5** GI tract: villous atrophy (small intestine), mucosal atrophy (colon and/or cecum), uterus weight↓, dehydration **Females 5** GI tract: villous atrophy (small intestine), mucosal atrophy (colon and/or cecum), uterus weight↓, mandibular lymph node: hyperplasia, dehydration, WBC↑, BW↓, Ala/Asp↑ **All doses** Red/dry/flaking, scrabbed skin and/or dry fur, skin: decreased thickness in tongue, larynx, esophagus, stomach, cervix, vagina (females only)	NOAEL: 10 mg/kg males 5 mg/kg females

Dog / beagle WIL-69513 (GLP)	5/sex/group: 3/sex/group for end-of-dosing + 2/sex/group recovery	0, 0.5, 1, 2 oral for 28 days with the exception of 2 males at 2 mg/kg (only 26 days) due to bad condition	**0.5 mg/kg** F: pituitary gland weight↓, epithelial atrophy of tongue, esophagus, stomach, rectum, salivary gland, **1 mg/kg** F: pituitary gland weight↓, epithelial atrophy of the eyes, decreased cellularity in thymus, M: fibrinogen↑, skin inflammation **2 mg/kg** F: pituitary gland weight↓, M: prostate weight↓, mixed-cell infiltrates in submucosa of the tongue **All doses** Ocular: nictitating membrane, clear and/or green discharge, injected sclera, complete and/or complete closure of the eyes), oral: clear material around the mouth, reddened gums, emesis, excreta: soft or mucoid faeces, diarrhoea, BW↓, RBC↓, albumin↓, ovary weight↓, spleen weight↓, thymus weight↓, M: testes weight↑	HNSTD 1 mg/kg
Dog / beagle 800235 3 GLP	6/sex/group: 4/sex/group for end-of-dosing + 2/sex/group recovery	0, 0.25, 0.5, 1, oral for 13 weeks with the exception of all males at 1 mg/kg	**0.25 mg/kg** **0.5 mg/kg** 1M dosing interruption due to poor condition between days 64 and 70, FC↓, M: increased lymphoid cellularity in the mandibular lymph node, mucosal atrophy of the uterus, decreased epithelial thickness of the cornea **1 mg/kg** M: all animals had to be euthanised, FC↓, lymphocytes↑, F: fibrinogen↑ **All doses** Gastrointestinal distress, red and/or dry skin, ocular changes, inflammation, decreased epithelial thickness in tongue, esophagus, larynx, cervix, vagina, perianal skin, WBC↑, albumin↓	NOAEL 0.25 mg/kg for males 1.0 mg/kg for females

The principle histopathological findings in the pivotal repeat dose toxicity studies in rats and dogs comprised the gastrointestinal tract (atrophy, single cell necrosis, mononuclear cell infiltration), reproductive system (atrophy and single cell necrosis), haematological system (acute phase response), and the squamous epithelium (decreased thickness) in multiple organs, such as skin and cavity. GI effects were generally dose-dependent with increases in incidence and severity in longer duration studies. The dose-limiting findings were reduced food consumption accompanied by body weight loss. Of note are the ocular clinical signs and ophthalmology findings which were known side effects also of osimertinib (Tagrisso). The gastrointestinal, dermal, and effects on epithelium of other organs were generally reversible after dose cessation. Based on plasma exposure levels and expected human exposure level at the intended therapeutic dose, there are no margins of safety.

3.2.4.3. Genotoxicity

A standard battery of *in vitro* and *in vivo* genotoxicity tests was performed with mobocertinib. Main study details and results are summarised in the table below:

Table 3.2.4.3.1: Genotoxicity studies with mobocertinib

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/ equivocal**
Gene mutations in bacteria 9601435 GLP	Salmonella strains TA1535, TA1537, TA98, TA100 + E. coli WP2uvrA	5 - 5000 µg/plate +/- S9	Negative
Chromosome Aberration Test 9601436 GLP	Human Lymphocytes	0 – 32 µg/mL +/- S9	Negative
Micronucleus assay in vivo 9800556 GLP	Rat, micronuclei in bone marrow immature erythrocytes	0, 60, 100, 300, 500 mg/kg	Negative

Mobocertinib showed no evidence for a genotoxic potential.

3.2.4.4. Carcinogenicity

As this application is for the use of mobocertinib for the treatment of patients with advanced NSCLC no carcinogenicity studies were submitted, which was considered acceptable.

3.2.4.5. Reproductive and developmental toxicity

No study on fertility and early embryonic development and on pre- and post-natal development were conducted with mobocertinib. This is in line with the ICH S9 guideline (Nonclinical Evaluation for Anticancer Pharmaceuticals). The effect of mobocertinib on fertility was assessed in single and repeat-dose toxicity studies in rat and dog. Reproductive organ changes included decreases in organ weights affecting the seminal vesicle/prostate gland, epididymides, uterus, and ovary/oviduct (in the rat) and reversible microscopic changes (atrophy and decreased epithelial thickness) in the uterus, cervix and vagina, testis and epididymis (in the dog).

The reproductive and developmental toxicity of mobocertinib was evaluated in an embryo-foetal development studies in rats.

Information available from general toxicology studies on the pharmaceutical's effect on reproductive organs should be used as the basis of the assessment of impairment of fertility. The applicant did not present data from the general toxicity study on potential effects on spermatogenesis as reduction in sperm count, alterations to sperm motility or morphology. In vivo animal studies with other tyrokinase inhibitors have shown dose-related effect on spermatogenesis. Nevertheless, the applicant has discussed the effects seen in the repeated dose studies and believes that generating additional animal data would not change the risk benefit discussion, as an impact on spermatogenesis is a known potential liability for some tyrosine kinase inhibitors. This is acknowledged.

A preliminary embryofoetal development study in pregnant rats identified that mobocertinib, similar to other EGFR inhibitors, has the potential for embryofoetal toxicity. Embryofoetal development findings consisted of embryolethality, and adverse effects on foetal growth (decreased foetal weight). Additionally, there was evidence of maternal toxicity (decreased body weight). There was no clear evidence of teratogenicity. The margin of safety is less than 1.

A pre- and postnatal toxicology study was not performed and is generally not warranted to support clinical trials or for marketing of pharmaceuticals for the treatment of patients with advanced cancer.

Exposure and distribution data in lactating animals and in offspring (including milk excretion) have not been evaluated. The applicant's proposal for the section 4.6 in the SmPC is generally acceptable. However, minor changes are suggested.

3.2.4.6. Toxicokinetic data

Plasma levels of mobocertinib and its metabolites AP32960 and AP32914 were evaluated in all the repeat-dose toxicity studies. In the 3-month rat study, the NOAEL produced an AUC of up to 1.5 times the human AUC. In the 3-month dog study, the NOAELs for males and females produced an AUC of 0.2 and 1.1 times the human AUC, respectively. For the 2 active metabolites, AP32960 and AP32914, exposures at animal NOAELs were up to 0.6 and 2.0 times the human AUC, respectively, indicating lack of margins of safety.

3.2.4.7. Tolerance

No local tolerance studies were submitted as the drug will be administered orally.

3.2.4.8. Other toxicity studies

In addition to monitoring the toxicological profile of mobocertinib and its two active metabolites, an additional study was performed in order to evaluate the potential toxicity and toxicokinetic (TK) profile of mobocertinib alone and in comparison to the combination of mobocertinib and the process intermediate ML00952187 (at 1% of the 160 mg clinical dose), when administered as a solution in 25 mM citrate buffer (pH 2.75) daily by oral gavage for 14 days to Sprague-Dawley rats. The findings in the mobocertinib/ML00952187 dose group were consistent with those observed with mobocertinib alone in the rat study with the following noteworthy exceptions: increased cellularity in the bone marrow, seminiferous tubule degeneration in the testes, and reduced sperm with cellular debris in the epididymis.

Impurities

The control of mutagenic impurities in the drug substance is consistent with the principles outlined in accordance with *ICH S2(R1): Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*. The potential mutagenic impurities were assessed for the starting materials, intermediates. All impurities that have been observed in drug substance batches were below their proposed acceptance criteria.

For the entire drug substance process, several potential impurities were identified as potential mutagenic impurities based on identification as alerts for mutagenicity, using *in-silico* analyses. All compounds are controlled at the process intermediate stage through either process design, testing and/or acceptance criteria.

All observed starting materials, reagents, solvents, intermediates, and associated process impurities were assessed with DEREK and Case Ultra (see also quality part).

Phototoxicity

Mobocertinib showed no evidence of phototoxic potential in an in vitro cytotoxicity assay conducted in the presence and absence of UV light.

3.2.5. Ecotoxicity/environmental risk assessment

The applicant provided an environmental risk assessment phase I.

Summary of main study results

Substance (INN/Invented Name): mobocertinib			
CAS-number (if available): 1847461-43-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 (pH 4 & 7) & OECD 123 (pH 9)	1.6 (pH = 4) 2.9 (pH = 7) 5.2 (pH = 9)	Potential PBT Y
PBT-assessment pending			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.2 (pH = 9)	Pot B
	BCF	Pending	B/not B OPEN
Persistence	DT50 or ready biodegradability	Pending	P/not P OPEN
Toxicity	NOEC or CMR	Pending	T/not T Open
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT **OPEN**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (prevalence)	0.0031	µg/L	< 0.01 threshold N
Other concerns (e.g. chemical class)			N

3.2.6. Discussion on non-clinical aspects

Pharmacology

Exon 20 insertion mutations in EGFR create a narrower binding pocket as compared to the wild-type receptor. Mobocertinib was designed to fit into the binding pocket of EGFR with exon 20 insertion mutations. It covalently binds to wild-type and exon 20 insertion mutant EGFR at Cys797. Thereby mobocertinib exhibits higher selectivity for exon 20 NPG EGFR over wild-type EGFR.

The specificity of mobocertinib was evaluated on a large panel of protein kinases including mutant variants. All 14 members of the EGFR family and BLK were inhibited with IC_{50} values under 2 nM. Six additional kinases (JAK3, TXK, BTK, BTK [E41K], BMX, and ACK1) were inhibited with IC_{50} lower than 20 nM. Mobocertinib metabolites AP32960 and AP32914 exhibited similar activity. AP32914 was in general more potent than the parent drug and AP32960 was slightly less active. The selectivity of mobocertinib for mutant over wild-type EGFR was also studied in cellular assays.

Mobocertinib inhibited WT EGFR phosphorylation with IC_{50} of 35 nM. For mutant variants, inhibition of proliferation of cells expressing EGFR with the respective mutations was evaluated. Mobocertinib reduced viability of cells featuring EGFR with exon 19 deletion and an L858R exon 21 mutation and those containing exon 20 activating insertions with IC_{50} values below 22 nM. The metabolites had similar activity profiles. The applicant concluded that mobocertinib was more potent against mutant variants than against WT EGFR. To further support this conclusion, the applicant has provided a literature report of the study in the Ba/F3 cell system engineered to overexpress either WT-EGFR or mutant EGFR (Vasconcelos et al. 2021). It clearly demonstrates that mobocertinib inhibits the cell viability of Ba/F3 cells dependent on EGFR exon 20 insertion mutants more efficiently (IC_{50} values

being between 63 and 203 nM) compared to Ba/F3 cells overexpressing WT-EGFR (IC_{50} = 763 nM). Cell growth inhibition by mobocertinib in the study by Vasconcelos et al. required 5- to 10-fold higher drug concentrations as compared to study ARP553 where also Ba/F3 cells engineered to express the same exon 20 insertion mutants were used (IC_{50} for mutant EGFR between 12 and 22 nM). The applicant provided a comparison of 2 different methodologies that were used for the generation of the engineered Ba/F3 cells, together for the 2 approaches used for testing their inhibition which, together could be the underlying reason for obtaining different IC_{50}. Both studies showed a stronger inhibition of the EGFR variants than the WT EGFR, suggesting a therapeutic window in the clinic is requested to explain this discrepancy in the context of the clinical efficacy taking into account the unbound clinical concentration of mobocertinib (**OC**).

Mobocertinib inhibited proliferation of LU0387 cells, a patient-derived NSCLC cell line expressing an EGFR exon 20 NPH insertion mutant, with a similar potency as afatinib but much better than erlotinib and gefitinib. Mobocertinib also reduced survival of NSCLC cell lines with exon 19 deletion, with L858R mutation, and with L858R plus a T790M resistance mutation with IC_{50} values in low nanomolar range. Due to its binding to Cys805 of HER2, mobocertinib exhibited high activity in cells with HER2 harbouring exon 20 insertions, exon 20 point mutation and non-exon 20 point mutations demonstrating IC_{50} in low nanomolar range.

In a patient-derived xenograft mouse model based on the above-mentioned LU0387 cell line, a dose-dependent statistically significant inhibition of tumour growth was achieved. The oral dose of 30 mg/kg even led to almost complete tumour regression. In a murine xenograft model based on human NSCLC H1975 cell line expressing an EGFR-L858R/T790M double mutant and a mouse xenograft model with an exon 20 ASV EGFR mutant as well as in mice bearing HER2 exon 20 mutant xenografts, mobocertinib also induced tumour regression at higher doses. The treatments were mostly well tolerated. Mobocertinib efficacy generally correlated with drug plasma levels. Levels of AP32914 were normally somewhat lower, and levels of AP32960 slightly higher, than those of the parent drug.

Mobocertinib selectivity for exon 20 insertion mutant over wild-type EGFR was supposed to reduce dose-limiting toxicities associated with WT EGFR inhibition. Western blot analysis of EGFR phosphorylation in lung tissues of mice treated with similarly efficacious doses of mobocertinib and afatinib showed persistent pronounced reduction in WT EGFR phosphorylation after afatinib treatment in contrast to mobocertinib, which appeared to only reversibly inhibit WT EGFR. Western blot is known to be a semi-quantitative method with high variability. Therefore, the applicant has supported the conclusion regarding lower inhibitory potency of mobocertinib towards WT EGFR compared to afatinib by the results of the immunoassay of EGFR phosphorylation in A431 cells. Although A431 are epidermoid carcinoma cells and lung tissues of healthy animals (thus, much more suitable than cancer cells for addressing the safety profile) were analysed only with Western Blot, the conclusion is generally agreed.

Study results demonstrated inhibitory effect of mobocertinib on EGFR harbouring the T790M substitution in exon20 that is associated with resistance towards several first and second generation EGFR inhibitors. Similarly, due to irreversible binding of mobocertinib to cysteine 797 (C797) in the EGFR kinase domain it is likely that the emergence of a mutation would impair mobocertinib therapeutic activity in the clinic. Regarding the impact of EGFR exon 20 insertion variant types on mobocertinib clinical efficacy, it was not possible to conclude but a more definite conclusion may be possible with increasing number of patients. The applicant is therefore asked to submit relevant data regarding the impact of T790M and other co-occurring mutations, as well as the gene resistance to mobocertinib, when results are available from ongoing clinical studies (**OC**).

In an off-target activity screening assay, mobocertinib was an antagonist of two receptors at concentrations higher than 5 µM. AP32960 and/or AP32914 were antagonists, inhibitors, or blockers of

seven targets at concentrations exceeding 1 µM. These concentrations are much higher than the clinically achieved C_{max}. Therefore, the identified off-target interactions are considered not clinically relevant.

Mobocertinib, AP32914 and AP32960 inhibited the hERG current with IC_{50} values between 5.1 and 10 µM, which is much higher than the clinical steady-state C_{max} of mobocertinib, AP32960 and AP32914 (120.2, 8.7 and 71.0 nM, respectively). In toxicology studies in rats and dogs with C_{max} values up to 118 nM, no drug-related effects on cardiovascular system were observed. However, mobocertinib induced QT prolongation in humans. The mechanism is unknown, since mobocertinib had no marked effects on hERG channels and on the ECG of dogs. In order to study the torsadogenic potential of mobocertinib, the applicant has agreed to investigate effects of mobocertinib on other cardiac ion channels involved in QT interval prolongation (Cav1.2, KvLQT1/minK and Nav1.5). In addition, the applicant has agreed to assess the potential of mobocertinib to induce early afterdepolarisations (EADs) in a non-GLP-compliant human IPSC-derived cardiomyocyte multi-electrode array (MEA) assay. Both studies will be performed post-marketing. This is acceptable, howerver, the applicant is requested to provide the intended time schedule for these studies (**OC**).

Pharmacokinetics

The LC-MS/MS methods for the analysis of mobocertinib, its active metabolites and its dimer in rat and dog plasma were developed and in general successfully validated. Although rather wide acceptance criteria were set for the validation of the dimer quantification methods, a critical analysis of the bioanalytical data from toxicokinetic rat and dog studies revealed that the accuracy and precision of the QC samples and the back-calculated standards were largely within the acceptance criteria set by the EMA.

Pharmacokinetics of mobocertinib, either as a free base or as a succinate salt (clinically relevant form), after intravenous administration was characterised by high volume of distribution in all species investigated. The systemic clearance was high in rodents and low in non-rodents. Consequently, half-life of the drug was short in mice, moderate in rats and very long in dogs. Following oral dosing of mobocertinib as a free base or as succinate, the drug showed rapid absorption in mice, moderate absorption in rats and moderate to low absorption in dogs. In all species studied, oral bioavailability was moderate, with exception of mobocertinib salt in rats having low bioavailability.

Protein binding of mobocertinib is very high and exceeds 99%. The same holds true for AP32960 and AP32914, although the bound fraction of the latter metabolite was somewhat lower. Mobocertinib and AP32960 showed no preferential distribution into red blood cells over plasma in mouse, rat, dog, and human blood. In a distribution study, relatively high tissue concentrations were found in liver, adrenal gland cortex, adrenal gland (entire), kidney outer medulla, small intestine, eye uvea, and thyroid. At the last observation time point, very high radioactivity remained in eye (uvea). Elimination of radioactivity from all tissues was generally very slow. [^{14}C]mobocertinib-related radioactivity appeared to be specifically, but reversibly, associated with melanin.

Mobocertinib is extensively metabolised in different species. In vitro, dealkylation, oxidation, and GSH conjugation were observed. No human-specific metabolites were found. Mobocertinib metabolism is primarily mediated by CYP3A4/5 with minor contribution from CYP2C8, CYP2C9 and CYP2D6. The active metabolites AP32914 and AP32960 were both further metabolised by CYP-dependent pathways, primarily by CYP3A4 and 3A5.

In vivo metabolism studies revealed a complex metabolic profile in rats and dogs. In the latter species, unchanged drug was the major component in plasma. The main overall metabolite in dogs was a cysteine conjugate of mobocertinib. Similarly to dog, the parent drug was the most abundant in rat plasma. Dealkylation and oxidation products, GSH adducts, and hydroxy-glucuronides were detected.

In humans, the same biotransformation pathways were noted. There was no single metabolite accounting for more than 10% of the total extracted circulating radioactivity. Therefore, toxicological evaluation of metabolites is not warranted.

Exposure to mobocertinib was 2.2- to 2.3-fold higher in female rats versus males. The applicant indicates that this is due to differences in metabolism. The observation of different exposure between sexes appears to be rat-specific as there were no such differences in dogs or in patients. It is agreed that the observed difference in exposure in female and male rats had low impact on toxicity data, since dosing in the 3-month repeat dose study in rats was modified. The lack of metabolism studies in female animals is thus considered acceptable.

In rats and dogs, most of radioactivity was excreted into faeces. Studies with bile-duct cannulated animals indicated that majority of faecal excretion was from biliary elimination. In both pre-clinical species investigated, renal excretion was minor and accounted for less than 10% of the dose.

In vitro experiments indicated that mobocertinib and both active metabolites (AP32960 and AP32914) are strong inducers of CYP3A4. Mobocertinib moderately induced CYP2C8 and was a weak inducer of CYP2B6 and 2C9. AP32914 weakly induced CYP1A2.

Mobocertinib was found to inhibit BCRP, P-gp, and OCT1 in vitro to an extent warranting in vivo studies. The applicant has predicted the effect of mobocertinib on the OCT1 substrate metformin in vivo using PBPK modelling. The PBPK model predicted no effect on metformin exposure but is not considered qualified for the purpose of simulating OCT1-driven DDIs. Based on current knowledge, OCT1 inhibition may impact the metformin response through altered hepatic distribution with little effect on plasma PK. In general, there is a lack of established sensitive OCT1 substrates, and the conduct of an *in vivo* PK study may not be feasible. Still, an effect on OCT1 substrates by mobocertinib cannot be ruled out. Section 5.2 of the SmPC should be updated to reflect that based on in vitro studies, mobocertinib is an inhibitor of OCT1 at clinically relevant concentrations (**OC**).

In addition, both in vitro and in vivo studies revealed mobocertinib potential to induce CYP3A4/5. As CYP3A4/5 induction is mediated by the pregnane X receptor (PXR), CYP2C is co-regulated and P-gp may be also induced. As PXR regulated enzyme interactions other than CYP3A4 has not been studied *in vivo*, the warning in section 4.5 of the SmPC should be retained: "Exkivity may also induce other enzymes and transporters (e.g., CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (e.g., pregnane X receptor activation)." (**OC**).

Furthermore, mobocertinib is an inhibitor of intestinal P-gp and BCRP. No clinical studies have been conducted to evaluate the effect of mobocertinib on substrates of these transporters in vivo, and the applicant has used PBPK modelling to predict the DDI potential. For the discussion of this issue, refer to Clinical AR / the clinical part of the Overview.

Toxicology

The wild-type EGFR is widely expressed in tissues of epithelial, mesenchymal and neuronal origin where it plays an important role in many physiological processes including proliferation, regeneration, differentiation and development. While mobocertinib is more potent towards mutant EGFR compared to wild-type EGFR as shown by in vitro PD studies, a greater potency towards mutant EGFR has not been shown in the in vivo experiments. Consequently, the repeat-dose toxicity findings are most likely related to inhibition of wild-type EGFR and are expected findings of mobocertinib. This is further supported by similar findings with other EGFR inhibitors.

The majority of the findings in the toxicology studies were seen below clinical exposures and it was not possible to calculate safety margins.

The main findings observed in repeat-dose toxicity studies in rats and dogs comprised the GI tract (including tongue), epithelial changes of skin (inflammation), eyes and cornea (atrophy, opacities – in dogs at ophthalmology examination), male and female reproductive tracts and the haematological system (acute phase response).

The findings present following 3 month of dosing were largely reversible within 1 month of cessation of dosing with the exception partial recovery of skin (rats and dogs), haematological and lymphoid system, GI tract, reproductive tract (male mammary gland in rats and cervix and vagina in dogs), and eyes (dogs only). The dose-limiting findings were reduced food consumption accompanied by body weight loss. Increases in white cell counts, decreases in red cell parameters and increased haematopoiesis in the spleen are considered to be secondary to the degenerative and inflammatory changes in these tissues. Similar findings have been seen with other EGFR TKIs and these are considered to be class effects. This might also be the case for the corneal changes found in dogs.

No study on fertility and early embryonic development and on pre- and post-natal development were conducted with mobocertinib. This is in line with the ICH S9 guideline (Nonclinical Evaluation for Anticancer Pharmaceuticals). The effect of mobocertinib on fertility was assessed in single and repeat-dose toxicity studies in rat and dog. Reproductive organ changes included decreases in organ weights affecting the seminal vesicle/prostate gland, epididymides, uterus, and ovary/oviduct (in the rat) and reversible microscopic changes (atrophy and decreased epithelial thickness) in the uterus, cervix and vagina, testis and epididymis (in the dog).

Information available from general toxicology studies on the pharmaceutical's effect on reproductive organs should be used as the basis of the assessment of impairment of fertility. The applicant did not present data from the general toxicity study on potential effects on spermatogenesis as reduction in sperm count, alterations to sperm motility or morphology. In vivo animal studies with other tyrokinase inhibitors have shown dose-related effect on spermatogenesis. Nevertheless, the applicant has discussed the effects seen in the repeated dose studies and believes that generating additional animal data would not change the risk benefit discussion, as an impact on spermatogenesis is a known potential liability for some tyrosine kinase inhibitors. This is acknowledged.

A preliminary embryofoetal development study in pregnant rats identified that mobocertinib, similar to other EGFR inhibitors, has the potential for embryofoetal toxicity. Embryofoetal development findings consisted of embryolethality, and adverse effects on foetal growth (decreased foetal weight). Additionally, there was evidence of maternal toxicity (decreased body weight). There was no clear evidence of teratogenicity. The margin of safety is less than 1. These findings are enclosed in the SmPC.

A pre- and postnatal toxicology study was not performed and is generally not warranted to support clinical trials or for marketing of pharmaceuticals for the treatment of patients with advanced cancer.

Exposure and distribution data in lactating animals and in offspring (including milk excretion) have not been evaluated. The applicant's proposal for the section 4.6 in the SmPC is generally acceptable. However, minor changes are suggested.

Mobocertinib was negative in a bacterial reverse mutation (Ames) assay, in an in vitro micronucleus assay, and in a rat in vivo micronucleus assay, indicating that mobocertinib does not present a genotoxic risk.

Carcinogenicity studies have not been performed with mobocertinib, which is considered acceptable in accordance with ICHS9. Mobocertinib did not cause genetic damage in *in vitro* and *in vivo* assays.

Mobocertinib did not elicit a phototoxic response in an in vitro neutral red uptake assay using BALB/3T3 mouse fibroblasts.

Environmental Risk Assessment

The provided PEC calculation including the refinement on prevalence is comprehensible and considered acceptable. References on prevalence were provided. No further risk assessment in Phase II is required.

There is no conclusion on the PBT assessment possible. The trigger value for PBT assessment is clearly exceeded at the pH of 9. Additionally, an ion-corrected logD can be calculated since mobocertinib most likely contains only one ionizable functional group (the dimethylamino group; pKa ≈ 9) within the environmentally relevant pH range (5-9). For pH 5 and 7 the ion-corrected logD can be calculated as ≈ 5.5 and ≈4.8, respectively. Therefore, a PBT assessment in a stepwise approach is deemed necessary. The applicant has proposed to provide a PBT assessment post authorisation. This is agreed by the assessor with respect to the anticipated study durations.

3.2.7. Conclusion on non-clinical aspects

Mobocertinib is a novel compound designed to specifically target EGFR with exon 20 insertion mutations. While pharmacological activity is promising, several concerns remain to be clarified.

Pharmacokinetics of mobocertinib was well characterised in pre-clinical models. Open issues are related to the drug interaction potential.

The toxicity of mobocertinib was evaluated in a serious of adequate studies using the clinical dosage form and clinical form of administration. Findings were in line with other EGFR inhibitors.

Environmental Risk Assessment

The available data do not allow to conclude definitively on the potential risk of mobocertinib to the environment. The applicant is kindly asked to provide a letter of commitment including an anticipated timetable for the update of the ERA.

3.3. Clinical aspects

Tabular overview of clinical studies

Table eff 1 List of clinical studies in support of the marketing authorisation application

Protocol Number	Protocol Title	Countries Involved
5.3.1.1 BA Study Reports		
TAK-788-1002	A Study to Assess Absolute Bioavailability (ABA) of TAK-788 and to Characterize Mass Balance, Pharmacokinetics (PK), Metabolism, and Excretion of Carbon-14 ([14C])-TAK-788 in Male Healthy Participants	USA
5.3.1.2 Comparative BA and BE Study Reports		
TAK-788-1001	A Study to Evaluate the Pharmacokinetics (PK), Safety and Tolerability of TAK-788 Followed by Evaluation of the Effects of a Low-Fat Meal on TAK-788 PK and Evaluation of Relative Bioavailability of TAK-788 Capsules in Healthy Participants	USA
TAK-788-1005	A Study to Evaluate the Effect of a High-Fat Meal on TAK-788 Pharmacokinetics (PK) in Healthy Adult Participants	USA
TAK-788-1003	A Phase 1/2 Study of the Oral EGFR/HER2 Inhibitor TAK-788 in Japanese Non-Small Cell Lung Cancer Patients	Japan
5.3.3.4 Extrinsic Factor PK Study Reports		

TAK-788-1006	A Phase 1 Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects	USA
TAK-788-1004	A Phase 1, 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	Australia, Netherlands, Singapore
5.3.5.2 Study Reports of Uncontrolled Clinical Studies		
AP32788-15-101 **(pivotal study)**	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	China, Japan, South Korea, Taiwan, USA, Germany, Spain, UK, Italy
TAK-788-5002 (supportive study)	Retrospective observational study of patients with NSCLC with EGFR exon 20 insertion mutations: real world data generation of natural history	N/A

Source: 'module 1.9 information relating to clinical trials'

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Mobocertinib (INN; ATC-code not yet assigned) is a small molecule kinase inhibitor of EGFR. During the development, it was also referred to as TAK-788 or AP32788.

Mobocertinib chemical name:

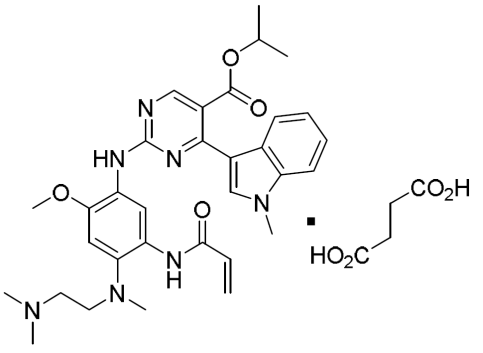
propan-2-yl 2-[5-(acryloylamino)-4-{[2-(dimethylamino)ethyl](methyl)amino}-2-methoxyanilino]-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate succinate

Molecular Formula: $C_{36}H_{45}N_7O_8$

Molecular Weight: 703.80 g/mol

Chirality: There are no chiral centres present for mobocertinib

Structural formula:



Clinical pharmacology program:

The objective of the clinical pharmacology program was to describe the PK of mobocertinib and its 2 active metabolites, AP32960 and AP32914, after oral administration.

Intrinsic and extrinsic factors that may affect the clinical pharmacology of mobocertinib were also assessed either by prospectively designed clinical pharmacology studies or by population PK and PBPK analyses of the PK data collected from clinical studies across the development program.

The clinical development programme for mobocertinib is summarised in the following table:

Table pk 1. Listing of Clinical Studies contributing to the Clinical Pharmacology of Mobocertinib

Study Identifier; (Title)	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)** **Dose Regimen(s) [a] ;** **Route of Administration**	**Number of Participants Enrolled**	**Healthy Participants or** **Diagnosis of Participants**	**Study Status; Type of Report**
AP32788-15-101 (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)	Safety, MTD, Efficacy **Characterize PK**	Phase 1/2, open-label, dose escalation(Part 1), RP2D expansion (Part 2) and pivotal extension (Part 3).	Mobocertinib orally QD in 28-day treatment cycles Part 1: Dose escalation starting dose: 5 mg/day MTD/RP2D: 160 mg QD Part 2: 160 mg QD Part 3: 160 mg QD	Parts 1 and 2: 210 Part 3: 97[a]	Part 1 dose escalation cohorts: adult patients with advanced NSCLC. Part 2 expansion cohorts at RP2D: 7 histologically and molecularly defined cohorts in adult patients with advanced NSCLC. Part 3 extension cohort: patients with locally advanced or metastatic NSCLC harboring EGFR exon 20 insertion mutations and had received at least 1 prior therapy.	Ongoing; CSR with data cutoff 29 May 2020
TAK-788-3001 (A Randomized Phase 3 Multicenter Open-label Study to Compare the Efficacy of TAK-788 as First-line Treatment Versus Platinum-Based Chemotherapy in Patients With Non–Small Cell Lung Cancer With EGFR Exon 20 Insertion Mutations)	Efficacy, Safety **Characterize PK**	Phase 3, open-label, randomized, controlled study of first-line treatment of adult patients with NSCLC with EGFR exon 20 insertion mutations.	Arm A: Mobocertinib 160 mg QD Arm B: Investigator's choice of either: Pemetrexed/cisplatin: pemetrexed (500 mg/m2) plus cisplatin (75 mg/m2) on Day 1 of a 21-day cycle. or Pemetrexed/carboplatin: pemetrexed (500 mg/m2) plus carboplatin, at a dose calculated to produce an AUC of 5 mg*min/mL on Day 1 of a 21-day cycle	Planned enrollment: 318	Adult patients with NSCLC with EGFR exon 20 insertion mutations.	Ongoing; None

Study Identifier; (Title)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dose Regimen(s) [a] ; Route of Administration	Number of Participants Enrolled	Healthy Participants or Diagnosis of Participants	Study Status; Type of Report
TAK-788-1001 (Phase 1, 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)	Safety, PK, Relative BA, Low-Fat **Food Effect**	Phase 1, 3-part, randomized, double-blind, placebo-controlled, or open-label crossover PK and safety study	Part 1: Single rising doses of mobocertinib starting at 20 mg, escalating to 40, 80, 120, and 160 mg Part 2: Single dose of mobocertinib 120 mg or 160 mg on Day 1 and 8 with or without a low-fat meal Part 3: Single dose of mobocertinib 160 mg on Day 1 and 8 as different drug products	75	Healthy adult subjects	Completed; Final
TAK-788-1002 (A Phase 1 Study to Assess Absolute Bioavailability of TAK-788 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]-TAK-788 in Male Healthy Subjects)	Absolute BA, mass balance, human **ADME**	Phase 1, open-label, 2-period, PK study	Period 1: Single oral dose of mobocertinib 160 mg on Day 1 IV microdose [^{14}C]-mobocertinib 50 µg (~2 µCi) on Day 1 (3.75 hours post oral dosing) Period 2: Single dose [^{14}C]-mobocertinib 160 mg (~100 µCi) as an oral solution	7	Healthy adult male subjects	Completed; Final
TAK-788-1003 (A Phase 1/2 Study of the Oral EGFR/HER2 Inhibitor TAK-788 in Japanese Non-Small Cell Lung Cancer Patients)	Safety, tolerability, PK, efficacy in a **Japanese population**	Phase 1/2, open-label, multi-center, dose escalation study	Phase 1 Part Dose escalation: mobocertinib starting at a dose of 40 mg QD and increasing until 160 mg QD Phase 2 Part Mobocertinib 160 mg QD	Part 1: 20 Part 2: Ongoing Planned enrollment: 30	Japanese adult patients with local advanced or metastatic NSCLC	Part 2 is ongoing; Final CSR for Part 1

Study Identifier; (Title)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dose Regimen(s) [a] ; Route of Administration	Number of Participants Enrolled	Healthy Participants or Diagnosis of Participants	Study Status; Type of Report
TAK-788-1004 (A Phase 1, 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)	**DDI** with midazolam	Phase 1, 2-part, open-label, PK study	Part A (Cycle 1, PK cycle): Oral midazolam 3 mg on Days 1 and 24 IV midazolam 1 mg on Days 2 and 25 Mobocertinib 160 mg QD on Days 3 to 30 Part B (Cycle 2 to 24): Mobocertinib 160 mg QD	Planned enrollment: 26	Patients with locally advanced or metastatic NSCLC	Completed; Final
TAK-788-1005 (A Phase 1, Randomized, 2-Period, 2-Sequence, Crossover Study to Evaluate the Effect of High-Fat Meal on TAK-788 Pharmacokinetics in Healthy Adult Subjects)	High-Fat **Food Effect**	Phase 1, open-label, randomized, crossover PK study	Single dose of mobocertinib 160 mg on Days 1 and 11 with or without a high-fat meal	14	Healthy adult subjects	Completed; Final
TAK-788-1006 (A Phase 1 Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects)	**DDI** with strong CYP3A inhibitor (itraconazole) or strong CYP3A inducer (rifampin)	Phase 1, open-label, 2-part, PK study	Part 1 Single dose of mobocertinib 20 mg on Period 1 Day 1 and Period 2 Day 5 Oral itraconazole 200 mg QD on Period 2 Days 1 to 14 Part 2 Single dose of mobocertinib 160 mg on Period 1 Day 1 and Period 2 Day 7 Oral rifampin 600 mg QD on Period 2 Days 1 to 13	24	Healthy adult subjects	Completed; Final
TAK-788-1007 (A Phase 1 Pharmacokinetic Study of Oral TAK-788 in Subjects with Severe Renal Impairment and Normal Renal Function)	Effect of severe **renal impairment** on PK	Phase 1, open-label, parallel-group, PK study	Single dose of mobocertinib 80 mg	Planned enrollment: 24	Adult healthy subjects with either severe renal impairment or normal renal function	Ongoing; None

Study Identifier; (Title)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dose Regimen(s) [a]; Route of Administration	Number of Participants Enrolled	Healthy Participants or Diagnosis of Participants	Study Status; Type of Report
TAK-788-1008 (Phase 1 Pharmacokinetics and Safety Study of Oral TAK-788 in Subjects with Moderate or Severe Hepatic Impairment and Normal Hepatic Function)	Effect of moderate or severe **hepatic impairment** on PK	Phase 1, open-label, parallel-group PK study	Single dose of mobocertinib 40 mg	Planned enrollment: 24	Adult healthy subjects with moderate hepatic impairment, severe hepatic impairment, or normal hepatic function	Ongoing; None

ADME: absorption, distribution, metabolism, excretion; AUC: area under the curve; BA: bioavailability; CYP: cytochrome P450; DDI: drug-drug interaction; EGFR: epidermal growth factor receptor; IV: intravenous; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; PK: pharmacokinetics; QD: once a day; RP2D: recommended phase 2 dose.

[a] Number of patients/subjects as of August 2020.

Formulations used during clinical development/commercial product:

All of the clinical studies were (or are being) conducted with immediate-release oral capsules except for Study TAK-788-1002, in which a microdose IV injection and an oral solution were also used. Mobocertinib capsules are an immediate-release oral dosage form containing mobocertinib drug substance as a "drug in capsule" ("DiC") with no excipients. One formulation of mobocertinib DiC, differing in the manufacturing process used to prepare the drug substance (ie, Process A, B, and C, see drug substance part of the Quality AR for details) and 3 dose strengths (5 mg, 20 mg, and 40 mg), was used during the clinical development of mobocertinib. One dose strength (40 mg) of mobocertinib DiC-C in a size 1 capsule has been used in the phase 2 pivotal extension phase of clinical Study AP32788-15-101 Part 3. The commercial product will be DiC-C in a size 2 capsule.

Mobocertinib doses investigated:

The initial dose escalation portion of Study AP32788-15-101 (Part 1) investigated mobocertinib total daily doses from 5 to 180 mg. The maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) was determined to be 160 mg QD, and this dosage was evaluated in Part 2 and Part 3 of Study AP32788-15-101.
Single doses from 20 to 160 mg mobocertinib were evaluated in the healthy subject studies.
According to the submitted SmPC, the recommended dose of mobocertinib is 160 mg Exkivity once daily. Exkivity treatment should be continued until disease progression or is no longer tolerated by the patient. The SmPC recommends dose modifications based on individual safety and tolerability.

Absorption

- ***Healthy subjects***

TAK-788-1001 (Part 1)

Study title Phase 1, 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

Study design The methodologies used in this study were randomized, double-blind, placebo-controlled, single rising dose, effects of a low-fat meal, and bioequivalence.

Part 1: Eight (8) healthy subjects were randomized in each dose cohort so that 6 subjects received a single dose of mobocertinib under fasted conditions and 2 subjects received placebo. The starting dose was 20 mg and the dose was escalated with each subsequent 8-subject cohort at dose levels of 40, 80, 120, and 160 mg. Dose escalation occurred if there were no dose-limiting toxicities after administration of mobocertinib and all Grade ≥ 2treatment-related adverse events resolved to Grade ≤1 or returned to baseline within 15 days before proceeding to the next planned higher dose. Intensive PK samples were collected from pre-dose to 168 hours post-dose in each healthy subject

Part 2: Six healthy subjects received single oral doses of 120 mg mobocertinib as an exploratory assessment, and 10 healthy subjects received single oral doses of 160 mg mobocertinib under fasted conditions and after consumption of a low-fat meal containing ≤350 calories and ≤15% calories from fat. Subjects were randomized to a crossover sequence at a 1:1 ratio and were administered mobocertinib under either fasted or low-fat meal conditions on Day 1 and again under the alternative food intake condition on Day 8. PK samples were collected at prespecified time points up to 168 hours postdose after mobocertinib administration on Day 1 and Day 8.

Part 3: Twelve (12) healthy subjects were randomly assigned to a crossover sequence at a 1:1 ratio to receive a single dose of mobocertinib DiC-A or DiC-B on Day 1 under fasted conditions, and the alternative DP on Day 8 under fasted conditions. PK samples were collected at prespecified time points up to 72 hours postdose after mobocertinib administration on Day 1 and Day 8.

Study objectives *Primary objectives*

Part 1: to assess safety and tolerability of TAK-788 and to identify a tolerable single oral dose of TAK-788 administered as a drug-in-capsule (DiC) formulation in healthy subjects.

Part 2: to characterize the effect of a low-fat meal on the PK of TAK-788 administered as a DiC formulation in healthy subjects.

Part 3: to evaluate the bioavailability of a test (Process B) DiC of TAK-788 relative to a reference (Process A) DiC of TAK-788 in healthy subjects.

Secondary objectives

Part 1: to characterize the PK of TAK-788 and its active metabolites, AP32960 and AP32914, administered as a DiC formulation in healthy subjects.

Part 2/Part 3: to assess the safety of TAK-788 following a single oral dose of TAK-788 in healthy subjects.

Additional Objectives:

Part 1: to evaluate the renal clearance of TAK-788 administered as a DiC formulation in healthy subjects.

Part 2/Part 3: to characterize the PK of active metabolites, AP32960 and AP32914, following a single oral dose of TAK-788 in healthy subjects.

Study period Date first subject signed informed consent form: 28 March 2018.

Date of last subject's last visit/contact: 18 January 2019.

Date of last subject's last procedure for collection of data for primary endpoint: 22 December 2018.

Date of last dose of study drug: 19 December 2018

No. of subjects Planned: Up to approximately 84 (approximately 56 in Part 1, up to 16 in Part 2, and up to 12 in Part 3).

Screened: 205 (108 in Part 1, 58 in Part 2, and 39 in Part 3).

Part 1: All 40 subjects were included in the randomized and safety analysis sets, and all 30 subjects who received study drug were included in the PK analysis set.

Part 2: All 16 subjects were included in the randomized, safety, and PK analysis sets.

Part 3: All 13 subjects were included in the randomized and safety analysis sets, and 1 subject was excluded from the PK analysis set.

Treatment Part 1: Single oral rising dose starting at 20 mg, escalating to 40, 80, 120, 160 mg. Placebo (0 mg capsules)

Part 2: Single oral doses of 120 and 160 mg.

Part 3: Single oral dose 160 mg DiC B (test) or 160 mg DiC A (reference).

Results

Mobocertinib/TAK-788

Descriptive statistics of plasma PK parameters of TAK-788 following single oral administration of TAK-788 at 20, 40, 80, 120 and 160 mg are provided in the table below:

Table pk 2. Summary of Plasma TAK-788 PK Parameters of Following Single Oral Dose Administration of TAK-788 to Healthy Subjects

TAK-788 PK Parameter (unit)	TAK-788 20 mg	TAK-788 40 mg	TAK-788 80 mg	TAK-788 120 mg	TAK-788 160 mg
N	6	6	6	6	6
t_{max} (h)	6.00 (2.00-8.08)	5.00 (4.00-6.00)	4.00 (4.00-8.00)	6.00 (2.00-6.00)	6.00 (4.00-6.00)
C_{max} (ng/mL)	3.22 (28.2)	7.85 (49.0)	14.7 (66.1)	25.8 (35.0)	52.2 (49.3)
AUC_{last} (h·ng/mL)	59.4 (11.8)	155 (62.2)	250 (65.5)	448 (38.0)	1010 (54.0)
AUC_{∞} (h·ng/mL)	63.6 (11.1)	160 (62.1)	257 (66.0)	456 (37.9)	1020 (53.8)
V_z/F (L)	8190 (15.7)	5740 (45.9)	6400 (57.0)	6940 (64.7)	4500 (24.8)
CL/F (L/h)	314 (11.9)	249 (49.5)	312 (72.0)	263 (56.9)	157 (33.2)
$t_{1/2z}$ (h)	18.1 (8.20)	16.0 (27.9)	14.3 (29.2)	18.3 (7.00)	19.9 (26.7)

AUC_{last}: area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration; AUC_{∞}: area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; CL/F: apparent clearance after extravascular administration; C_{max}: maximum observed plasma concentration; PK: pharmacokinetic; $t_{1/2z}$: terminal disposition phase half-life; t_{max}: time of first occurrence of C_{max}; V_z/F: apparent volume of distribution during the terminal disposition phase after extravascular administration.

Parameters are presented as geometric mean (%CV), except for tmax which is presented as median (range).

☐: PK Parameter after a single oral dose of 160 mg highlighted by the assessor

Source: Clinical Study Report TAK-788-1001; Table 11.i pg. 73/115

After single oral dose administration of TAK-788, geometric mean plasma TAK-788 C_{max} ranged from 3.22 ng/mL at 20 mg to 52.2 ng/mL at 160 mg. The median t_{max} was 4.00 to 6.00 hours across this

dose range. The geometric mean AUC_∞ values ranged from 63.6 h*ng/ml to 1020 h*ng/ml . Intersubject variability (%CV) for TAK-788 ranged from 28.2% to 66.1% for C_{max} and from 11.1%-66.0% for AUC_∞.

Metabolites AP32914 and AP32960

Descriptive statistics of plasma PK parameters of the active metabolites AP32914 and AP32960 following single oral administration of TAK-788 at 20, 40, 80, 120, and 160 mg are provided in the tables below:

Table pk 3. Summary of Plasma AP32914 PK Parameters Following Single Oral Dose Administration of TAK-788 to Healthy Subjects

AP32914 PK Parameter (unit)	TAK-788 20 mg	TAK-788 40 mg	TAK-788 80 mg	TAK-788 120 mg	TAK-788 160 mg
N	6	6	6	6	6
t_{max} (h)	ND	6.00 (4.00-8.00)	4.00 (4.00-8.00)	6.00 (6.00-6.00)	6.00 (4.00-6.00)
C_{max} (ng/mL)	ND	0.735 (29.2)	1.32 (66.2)	2.04 (30.3)	4.05 (43.3)
AUC_{last} (h·ng/mL)	ND	11.5 (47.8)	14.6 (68.3)	31.7 (33.9)	80.4 (53.8)
AUC_∞ (h·ng/mL)	ND	19.3 (16.0) [a]	20.3 (56.0) [b]	34.6 (31.6)	85.2 (52.2)
$t_{1/2z}$ (h)	ND	13.8 (23.8) [a]	12.2 (16.8) [b]	12.0 (9.6)	16.1 (27.4)

AUClast: area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration; AUC∞: area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; Cmax: maximum observed plasma concentration; PK: pharmacokinetic; t1/2z: terminal disposition phase half-life; tmax: time of first occurrence of Cmax.

Parameters are presented as geometric mean (%CV), except for tmax which is presented as median (range).

[a] N = 2.

[b] N = 5.

Source: Clinical Study Report TAK-788-1001; Table 11.j pg. 75/115

Table pk 4. Summary of Plasma AP32960 PK Parameters Following Single Oral Dose Administration of TAK-788 to Healthy Subjects

AP32960 PK Parameter (unit)	TAK-788 20 mg	TAK-788 40 mg	TAK-788 80 mg	TAK-788 120 mg	TAK-788 160 mg
N	6	6	6	6	6
t_{max} (h)	6.00 (2.00-8.08)	4.00 (4.00-6.00)	4.00 (2.00-6.00)	6.00 (6.00-6.00)	5.00 (4.00-6.00)
C_{max} (ng/mL)	1.55 (30.3)	3.48 (24.7)	8.30 (59.1)	13.4 (38.5)	25.4 (40.1)
AUC_{last} (h·ng/mL)	32.7 (19.3)	74.9 (28.3)	159 (44.9)	284 (41.1)	539 (34.9)
AUC_∞ (h·ng/mL)	37.4 (16.5)	79.8 (27.2)	166 (45.4)	293 (39.6)	548 (34.7)
$t_{1/2z}$ (h)	24.0 (14.3)	21.4 (13.8)	22.2 (5.10)	28.9 (20.1)	29.2 (21.3)

AUClast: area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration; AUC∞: area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; Cmax: maximum observed plasma concentration; PK: pharmacokinetic; t1/2z: terminal disposition phase half-life; tmax: time of first occurrence of Cmax.

Parameters are presented as geometric mean (%CV), except for tmax which is presented as median (range).

Source: Clinical Study Report TAK-788-1001; Table 11.k pg. 78/115

TAK-788-1002

Study title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-788 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]-TAK-788 in Male Healthy Subjects

Study design: This was an open-label, 2-period, single-dose study in healthy male subjects.

On Day 1 of Period 1 (Absolute Bioavailability [ABA] Study Period), after at least a 10-hour fast, 6 subjects received a single unlabeled oral 160 mg (4 x 40 mg) dose of mobocertinib as capsules. At 3.75 hours post oral dosing (ie, 15 minutes prior to the median tmax for the oral unlabeled dose (~4 hours), subjects received an IV microdose of [^{14}C]-mobocertinib as a 5 mL infusion over 15 minutes. The planned dose was 50 µg (~2 µCi) [^{14}C]-mobocertinib.

Serial blood sampling was performed and urine and feces were collected to determine the PK of mobocertinib and its metabolites (AP32960 and AP32914) in plasma, whole blood, and urine, and total radioactivity in plasma, whole blood, urine, and feces, and to characterize the metabolite profiles of mobocertinib in plasma, urine, and feces.

Subjects were to be confined in the clinic until a discharge criterion was met or up to 10 days postdose. The decision as to whether or not to discharge a subject who did not meet a discharge criterion by Day 11 was to be made on a case-by-case basis. After a discussion between the sponsor and the principal investigator, it was decided that subjects who did not meet a discharge criterion by Day 11 would continue with at-home fecal sample collections until a discharge criterion was met.

Any subject who experienced emesis within 8 hours post the oral dose in either Period 1 or 2 was excluded in the final data analysis and replaced with a new subject. If a subject had experienced emesis after dosing in Period 2, vomitus was to be collected as much as possible and assayed for total radioactivity.

Study objectives *Primary objectives*

Period 1 (Absolute Bioavailability [ABA])

To determine ABA of mobocertinib following single microdose intravenous (IV) administration of 50 µg (~2 µCi) [^{14}C]-mobocertinib and single oral administration of 160 mg mobocertinib.

Period 2 (Absorption, Distribution, Metabolism, and Elimination [ADME])

To assess the mass balance (ie, cumulative excretion of total radioactivity in urine and feces) and metabolite profile of mobocertinib in plasma, urine, and feces following a single oral administration of 160 mg (~100 µCi) [^{14}C]-mobocertinib solution.

To characterize the pharmacokinetics (PK) of mobocertinib and its metabolites (AP32960 and AP32914) in plasma, whole blood, and urine, and total radioactivity concentration equivalents in plasma and whole blood following a single oral solution dose of 160 mg (~100 µCi) [^{14}C]-mobocertinib.

Secondary objectives

To determine the PK of [^{14}C]-mobocertinib and its metabolites (AP32960 and AP32914) following a single IV administration of 50 µg [^{14}C]-mobocertinib and the PK of mobocertinib and its metabolites (AP32960 and AP32914) following a single oral administration of 160 mg mobocertinib.

Period 1 (ABA) and 2 (ADME)

To assess the safety of mobocertinib during the ABA and ADME study periods.

Exploratory Objective:

	Period 1 (ABA) To determine parent [^{14}C]-mobocertinib biliary excretion into feces and urinary excretion following a single IV administration of 50 µg (~2 µCi) [^{14}C]-mobocertinib.
Study period	Date first subject signed informed consent form: 22 January 2019 Date of last subject's last visit/contact: 11 March 2019
No. of subjects	Six participants planned; 6 participants were analysed for PK and 7 for safety.
Treatment	*Treatment A:* 160 mg mobocertinib in capsules administered at Hour 0 on Day 1 followed by 50 µg (~2 µCi) [^{14}C]-mobocertinib IV solution administered over 15 minutes from 3.75 to 4 hours following the oral dose (Period 1). *Treatment B:* 160 mg (~100 µCi) [^{14}C]-mobocertinib oral solution administered at Hour 0 on Day 1 (Period 2).

Results

Period 1 (Absolute Bioavailability)

Plasma mobocertinib concentrations following oral dosing were detectable in 5 of 6 subjects by 0.5 hour postdose, in all subjects by 1 hour postdose, and remained quantifiable in all subjects through 72 hours postdose. Plasma [^{14}C]-mobocertinib concentrations normalized to a 160 mg dose following IV co-administration were detectable in all subjects at the end of infusion and remained quantifiable in all subjects through 32.25 hours following the start of IV infusion (i.e., 36 hours following oral dosing of mobocertinib). Arithmetic mean plasma concentrations of [^{14}C]-mobocertinib normalized to a 160 mg dose following IV co-administration were higher than those of plasma mobocertinib following oral dosing throughout the entire sampling interval, and declined in a multi-exponential fashion, exhibiting similar elimination profiles.

A summary of plasma mobocertinib, AP32960, and AP32914 PK values following a single oral dose of 160 mg mobocertinib in healthy male subjects is presented in the table below:

Table pk 5. Summary of Plasma TAK-788, AP32960, and AP32914 Pharmacokinetics Following Administration of a Single Oral Dose of 160 mg TAK-788 in Healthy Male Subjects (Period 1)

Pharmacokinetic Parameter	TAK-788 N=6	AP32960 N=6	AP32914 N=6
t_{max} (hr)	5.00 (4.00, 6.00)	4.50 (4.00, 6.00)	5.00 (4.00, 6.00)
C_{max} (ng/mL)	56.7 (52.2)	23.3 (21.2)	4.09 (36.0)
AUC_{∞} (ng*hr/mL)	1050 (64.9)	478 (30.6)	73.0 (53.2)
$t_{1/2z}$ (hr)	22.9 (17.9)	29.1 (18.2)	12.5 (37.5)
CL/F (L/hr)	152 (64.9)	NA	NA
V_z/F (L)	5030 (53.6)	NA	NA
Molar AUC_{∞} M:P Ratio	NA	0.466 (33.9)	0.0712 (23.1)

t_{max} values are presented as median (minimum, maximum).
Cmax, AUC_{∞}, $t_{1/2z}$, CL/F, V_z/F, and Molar AUC_{∞} M:P Ratio values are presented as geometric mean (geometric percent coefficient of variation).
NA = Not applicable

Source: TAK-788-1002 CSR; Tab 11.e pg. 78/113

A summary of absolute bioavailability of mobocertinib following a single oral dose of 160 mg mobocertinib and a single IV infusion of 50 µg (~2 µCi) [^{14}C]-mobocertinib in healthy male subjects is presented in the table below:

Table pk 6. Summary of Absolute Bioavailability of TAK-788 Following Administration of a Single Oral Dose of 160 mg TAK-788 and a Single Intravenous Dose of 50 µg (~2 µCi) [14C]-TAK-788 Administered Over 15 Minutes From 3.75 to 4 Hours After the Oral Dose in Healthy Male Subjects (Period 1)

	160 mg TAK-788 PO (Test)		50 µg (~2 µCi) [^{14}C]-TAK-788 IV (Reference)				
Pharmacokinetic Parameter	Geometric LSM	n	Geometric LSM	n	%F	90% Confidence Interval	Intra-subject CV%
AUC_{∞} (ng*hr/mL)	913	6	2490	6	36.7	22.4 - 60.2	49.3

160 mg TAK-788 PO: Single Oral Dose of 160 mg TAK-788 (Test)
50 µg (~2 µCi) [^{14}C]-TAK-788 IV: Single Intravenous Dose of 50 µg (~2 µCi) [^{14}C]-TAK-788 (Reference)
AUC_{∞} for reference was normalized to a 160 mg dose.
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
%F = 100*(AUC_{∞} after oral administration/Dose normalized AUC_{∞} after IV infusion)
Intra-subject CV% was calculated as 100 x (square root(exp[MSE]$^{-1}$)), where MSE = Residual variance from ANOVA.
Source: TAK-788-1002 CSR; Tab 11.g pg. 80/113

Period 2 [ADME]

PK parameters of mobocertinib, AP32960 and AP32914 after administration of the 160 mg (~100 µCi) [^{14}C]-mobocertinib oral solution dose are presented in detail in the table below:

Table pk 7. Summary of Whole Blood and Plasma Mobocertinib, AP32960, AP32914, and Total Radioactivity (TRA) PK Parameters Following Administration of a Single Oral Solution Dose of 160 mg (~100 µCi) [^{14}C]-Mobocertinib in Healthy Subjects (Study TAK-788-1002 Period 2)

PK Parameter[a]	Mobocertinib N=6	AP32960 N=6	AP32914 N=6	TRA N=6
Whole Blood				
t_{max} (h)	5.01 (2.01-6.01)	5.01 (3.02-5.01)	5.01 (4.01-6.01)	24.0 (8.01-36.0)
C_{max} (ng/mL or ng eq/g)[b]	40.5 (29.1)	26.7 (10.6)	3.05 (28.6)	725 (14.6)
AUC_{last} (ng*h/mL or ng eq*h/g)[b]	718 (33.2)	543 (20.5)	45.7 (40.4)	131000 (18.5)
AUC_{∞} (ng*h/mL or ng eq*h/g)[b]	729 (32.8)	556 (20.2)	52.4 (37.3)	325000 (21.2)
$t_{1/2z}$ (h)	20.5 (25.4)	30.9 (12.1)	12.8 (23.1)	301 (28.1)
CL/F (L/h)	222 (32.6)	NA	NA	0.498 (20.7)
V_z/F (L)	6550 (18.0)	NA	NA	216 (23.7)
Molar AUC_{∞} M:P Ratio	NA	0.781 (12.3)	0.0736 (15.7)	NA
Molar AUC_{∞} Ratio (Analyte vs. TRA)	0.00224 (28.3)	0.00175 (21.6)	0.000165 (31.2)	NA
B:P Ratio C_{max}	0.794 (17.1)	1.18 (10.4)	0.713 (8.10)	NA
B:P Ratio AUC_{∞}	0.763 (17.7)	1.15 (10.2)	0.714 (7.60)	NA
Plasma				
t_{max} (h)	6.00 (3.00-6.00)	4.00 (3.00-5.00)	6.00 (3.00-6.00)	24.0 (8.02-36.0)
C_{max} (ng/mL or ng eq/mL)[b]	51.0 (34.9)	22.7 (19.8)	4.28 (34.7)	1250 (13.4)
AUC_{last} (ng*h/mL or ng eq*h/mL)[b]	945 (39.2)	471 (27.5)	63.6 (45.7)	230000 (15.5)
AUC_{∞} (ng*h/mL or ng eq*h/mL)[b]	956 (38.6)	486 (26.7)	73.4 (39.9)	556000 (14.9)
$t_{1/2z}$ (h)	22.8 (26.6)	30.5 (21.1)	14.0 (30.6)	281 (29.1)
CL/F (L/h)	169 (38.4)	NA	NA	0.292 (14.6)
V_z/F (L)	5560 (16.6)	NA	NA	118 (22.8)
Molar AUC_{∞} M:P Ratio	NA	0.520 (15.3)	0.0787 (15.1)	NA
Molar AUC_{∞} Ratio (Analyte vs. TRA)	0.00172 (31.1)	0.000896 (21.4)	0.000135 (36.1)	NA

AUC_{∞}: area under the concentration-time curve from time 0 to infinity; AUClast: area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; B:P ratio: blood-to-plasma ratio; Cmax: maximum observed concentration; CL/F; apparent oral clearance; M:P ratio: metabolite-to-parent ratio; NA: not applicable; PK: pharmacokinetic; $t_{1/2z}$: terminal disposition phase half-life; t_{max}: time of first occurrence of C_{max}; TRA: total radioactivity; V_z/F: apparent volume of distribution during the terminal disposition phase.
a Parameters are presented as geometric mean (geometric %CV), except for t_{max}, which is presented as median (range).
b Mass units of parameter values for mobocertinib, AP32960, and AP32914 are presented in ng and for total radioactivity (TRA) are presented in ng eq.
Source: 2.7.2 Clinical Pharmacology Studies; Tab 2.s pg. 85/179

Mobocertinib administered as an oral solution was readily absorbed and metabolized into AP32960 and AP32914. Median t_{max} values for mobocertinib, AP32960, and AP32914 were comparable in both plasma and whole blood at 4 to 6 hours postdose, whereas the median t_{max} value for total radioactivity was 24 hours in both whole blood and plasma. The small proportions of mobocertinib, AP32960, and AP32914 relative to total radioactivity circulating in whole blood is corroborated by the observed molar AUC_{∞} ratio of each analyte versus total radioactivity. Mobocertinib and its active metabolites, AP32960 and AP32914, were minor components in plasma, accounting for only 0.275% of total plasma radioactivity as the majority of mobocertinib-related material is covalently bound to plasma proteins. The covalent binding of mobocertinib and its metabolites to plasma proteins resulted in a limited amount of total radioactivity in plasma being characterised with a mean extraction recovery of 3.86%.

The blood-to-plasma C_{max} and AUC_{∞} ratios for mobocertinib, AP32960, AP32914, and combined molar exposure ranged from approximately 0.7 to 1.2, thereby indicating that mobocertinib, AP32960, and AP32914 did not show preferential distribution into human whole blood over plasma.

- ***Subjects with Non-Small Cell Lung Cancer***

TAK-788-101

[*Excerpt of the study design focused on the parts relevant for pharmacokinetic assessment*]

Study 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

Study design 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 pivotal 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).

The study is currently ongoing, with the end of study planned for 3 years after enrolment of the last patient, unless stopped earlier due to futility or sponsor decision.

Study objectives *Primary objectives*

Parts 1 and 2:

The objectives of this study for Parts 1 and 2 (dose escalation and expansion cohorts) were:

[…]

3. To determine the pharmacokinetic (PK) profile of mobocertinib and its active metabolites, AP32960 and AP32914.

[…]

Parts 3:

The primary objective of Part 3 of the study (extension cohort) was to determine the efficacy of mobocertinib, as evidenced by confirmed objective response rate (cORR), as assessed by the independent review committee (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.

Secondary objectives

[…]

3. To collect sparse plasma concentration-time data of mobocertinib and its active metabolites, AP32960 and AP32914, to contribute to population PK and exposure-response analyses.

[…]

Exploratory Objective:

[...]

The exploratory objectives of Part 3 of the study were:

[...]

4. To explore relationships between tumor and/or plasma/serum biomarkers and mobocertinib efficacy, safety, and/or CYP3A induction.

Study period Date first patient signed informed consent form: 08 June 2016

Date of last patient's last visit/contact: The study is ongoing. This report includes data collected for all patients through the data cut-off date of 29 May 2020.

No. of subjects Parts 1 and 2: Dose Escalation and Expansion Cohorts

Planned: 311 to 341 patients.

Enrolled: 260 patients.

Analyzed: Full analysis set (efficacy and safety): 209 patients. Efficacy analyses were conducted on individual cohorts, including the following cohort of note:

– Expanded refractory exon 20 cohort: 28 patients.

PK population: 209 patients.

Part 3: Extension Cohort

Planned: 91 patients.

Enrolled: 97 patients.

Analyzed: full analysis set (efficacy and safety): 96 patients, PK population: 96 patients, patient-reported outcome population: 90 patients.

[…]

Treatment The starting dose in Part 1 (dose escalation phase) was 5 mg taken orally QD. The total daily doses evaluated were 5 to 180 mg.

Patients in Part 2 (expansion cohorts) and Part 3 (extension cohort) received mobocertinib at the RP2D of 160 mg QD. Each 28-day dosing period was referred to as 1 cycle.

Results

Mobocertinib/TAK-788

The plasma PK parameters of mobocertinib on Cycle 1 Day 1 and Cycle 2 Day 1, are summarised in the table at the next page.

Table pk 8. Plasma PK Parameters of Mobocertinib Following Single Dose and Once Daily Oral Administration of Mobocertinib in Patients With NSCLC - Dose Escalation (Part 1) and Expansion Cohorts (Part 2)

	Mobocertinib Dose (mg)							
Parameter	**5**	**10**	**20**	**40**	**80**	**120**	**160**	**180**
Cycle 1 Day 1								
N	4	5	5	6	7	26	138	4
T_{max} (h) (range)	4.04 (3.97, 4.08)	3.95 (3.80, 6.00)	4.08 (2.00, 6.00)	4.02 (3.02, 6.05)	4.03 (1.98, 6.00)	4.00 (2.00, 6.17)	4.00 (1.07, 8.08)	3.95 (3.83, 5.93)
C_{max} (ng/mL) (%CV)	2.27 (74.8)	5.37 (14.3)	8.79 (57.2)	20.2 (59.5)	33.3 (78.4)	49.3 (53.4)	77.9 (61.0)	86.9 (46.1)
AUC_{24} (ng*h/mL) (%CV)	28.3 (59.8)	62.3 (15.0)	99.3 (70.6)	250 (64.9)	386 (69.5)	599 (61.4)[c]	972 (57.7)[g]	1050 (55.1)
Cycle 2 Day 1								
N	2	2	4	4	3	14	70	1
$T_{max,ss}$ (h) (range)	6.08, 7.83	2.00, 6.15	2.97 (1.08, 7.97)	5.04 (4.07, 8.00)	4.12 (4.00, 8.00)	4.10 (1.08, 7.83)	4.00 (0.00, 24.0)	1.83
$C_{max,ss}$ (ng/mL) (%CV)	2.11, 2.18	5.58, 5.97	7.70 (40.2)	19.3 (101)	22.4 (58.7)	52.9 (68.6)	70.4 (54.8)	64.8
$AUC_{24,ss}$ (ng*h/mL) (%CV)	34.2, 37.9	95.7, 104	105 (63.5)	294 (89.1)	321 (79.4)	772 (76.0)[d]	951 (53.0)[h]	768
R_{ac} for AUC_{24} (%CV)	1.90, 2.20	1.60, 1.64	1.07 (21.7)	1.46 (18.0)	1.52 (56.8)	1.25 (37.9)[e]	1.03 (55.0)[i]	1.14
Effective half-life (h) (%CV)	22.3, 27.4	17.0, 17.8	7.82 (48.8)[a]	14.1 (32.2)	23.0, 27.2[b]	15.4 (57.6)[f]	12.6 (66.8)[j]	7.96

%CV: percent coefficient of variation; AUC_{24}: area under the concentration-time curve from time 0 to 24 hours; $AUC_{24,ss}$: area under the concentration-time curve from time 0 to 24 hours, at steady state; C_{max}: maximum observed concentration; $C_{max,ss}$: maximum observed concentration during a dosing interval, at steady state; NSCLC: non–small-cell lung cancer; PK: pharmacokinetic; R_{ac}: accumulation ratio; t_{max}: time of first occurrence of C_{max}; $t_{max,ss}$: time of first occurrence of C_{max}, at steady state.

Parameters are presented as geometric mean (geometric %CV), except for tmax which is presented as median (range). Individual values are reported if N <3.

a N = 3; b N = 2; c N = 23; d N = 12; e N = 10; f N = 6; g N = 134; h N = 68; i N = 65; j N = 36.

☐: PK Parameter of the 160 mg dose at C1D1 and D2D1 highlighted by the assessor

Source: Clinical Study Report TAK-788-15-101; Table 17 pg. 109/285

Mobocertinib was absorbed into systemic circulation after oral administration, and the C_{max} of mobocertinib was observed at approximately 4 hours (median t_{max}) after the daily dose. While the terminal elimination half-life of mobocertinib could not be characterized due to the daily dose regimen, the geometric mean of effective half-life based on accumulation was in the range of 7.82 to 15.4 hours across 20 to 160 mg mobocertinib QD.

Active Metabolites AP32960 and AP32914

The plasma PK parameters of AP32960 and AP32914, the two active metabolites of mobocertinib formed by CYP3A, at Cycle 1 Day 1 and Cycle 2 Day 1 (Day 29 of continuous dosing) after oral administration of mobocertinib are summarised in the tables below:

Table pk 9. Plasma PK Parameters of AP32960 Following Single Dose and Once Daily Oral Administration of Mobocertinib in Patients With NSCLC - Dose Escalation (Part 1) and Expansion Cohorts (Part 2)

	Mobocertinib Dose (mg)							
Parameter	**5**	**10**	**20**	**40**	**80**	**120**	**160**	**180**
C1D1								
N	4	5	5	6	7	26	138	4
T_{max} (h) (range)	4.04 (3.97, 6.05)	3.95 (3.80, 5.92)	4.08 (2.00, 6.00)	4.06 (3.02, 6.05)	4.03 (2.00, 6.00)	4.00 (2.00, 24.3)	4.00 (1.83, 8.05)	4.91 (3.92, 5.93)
C_{max} (ng/mL) (%CV)	0.627 (58.1)	1.97 (27.5)	4.00 (48.7)	7.06 (27.8)	14.9 (69.4)	25.8 (42.4)	33.3 (47.6)	40.6 (11.4)
AUC_{24} (ng*h/mL) (%CV)	8.35 (51.8)	26.2 (42.0)	42.7 (56.6)	87.9 (27.8)	170 (49.9)	294 (45.4)[a]	423 (42.3)[d]	486 (21.7)
Molar AP32960 to mobocertinib AUC_{24} ratio (%CV)	0.302 (33.9)	0.432 (29.6)	0.441 (21.3)	0.360 (51.6)	0.450 (56.3)	0.502 (35.7)[a]	0.446 (32.8)[d]	0.473 (31.3)
C2D1								
N	2	2	4	4	3	14	70	1
$T_{max,ss}$ (h) (range)	6.03, 6.08	2.00, 4.08	4.08 (3.93, 7.97)	5.04 (4.07, 8.00)	4.12 (4.00, 8.00)	4.05 (1.08, 7.83)	4.00 (0.00, 24.0)	3.92
$C_{max,ss}$ (ng/mL) (%CV)	0.730, 1.09	2.30, 2.34	3.75 (48.8)	10.3 (44.2)	15.6 (60.6)	32.3 (49.7)	40.6 (44.5)	39.9
$AUC_{24,ss}$ (ng*h/mL) (%CV)	12.3, 18.5	40.0, 48.8	57.3 (77.2)	164 (40.0)	231 (88.9)	477 (59.1)[b]	572 (43.1)[e]	531
Molar AP32960 to mobocertinib AUC_{24} ratio (%CV)	0.333, 0.556	0.428, 0.480	0.559 (24.2)	0.571 (39.5)	0.738 (10.6)	0.633 (20.0)[b]	0.616 (21.5)[e]	0.709
R_{ac} for AUC_{24} (%CV)	2.25, 2.69	1.90, 2.32	1.34 (17.3)	1.88 (14.8)	1.80 (54.0)	1.59 (23.1)[c]	1.42 (49.9)[f]	1.33
Effective half-life (h) (%CV)	28.4, 35.9	22.3, 29.5	11.6 (39.4)	21.8 (22.8)	16.8 (138)	16.2 (41.6)[c]	15.3 (74.6)[g]	11.9

%CV: percent coefficient of variation; AUC_{24}: area under the concentration-time curve fom time 0 to 24 hours; $AUC_{24,ss}$: area under the concentration-time curve from time 0 to 24 hours, at steady state; C_{max}: maximum observed concentration; $C_{max,ss}$: maximum observed concentration during a dosing interval, at steady state; NSCLC: non–small-cell lung cancer; PK: pharmacokinetic; R_{ac}: accumulation ratio; t_{max}: time of first occurrence of C_{max}; $t_{max,ss}$: time of first occurrence of C_{max}, at steady state.

Parameters are presented as geometric mean (geometric %CV), except for tmax which is presented as median (range). Individual values are reported if N <3.

a N = 23; b N = 12; c N = 10; d N = 134; e N = 68; f N = 65; g N = 55.

☐: PK Parameter of the 160 mg dose at C1D1 and D2D1 highlighted by the assessor

Source: Clinical Study Report TAK-788-15-101; Table 18 pg. 112/285

Table pk 10. Plasma PK Parameters of AP32914 Following Single Dose and Once Daily Oral Administration of Mobocertinib in Patients With NSCLC - Dose Escalation (Part 1) and Expansion Cohorts (Part 2)

	mobocertinib Dose (mg)							
Parameter	**5**	**10**	**20**	**40**	**80**	**120**	**160**	**180**
C1D1								
N	4	5	5	6	7	26	138	4
T_{max} (h) (range)	4.04 (3.97, 7.92)	3.95 (3.80, 6.00)	4.08 (2.00, 6.00)	5.00 (3.02, 6.05)	4.05 (2.00, 23.1)	4.00 (2.07, 24.3)	4.08 (1.83, 24.5)	4.91 (3.92, 5.93)
C_{max} (ng/mL) (%CV)	0.216 (63.9)	0.436 (38.5)	0.760 (58.7)	1.38 (38.1)	2.35 (75.7)	3.16 (62.6)	4.53 (56.6)	6.31 (15.5)
AUC_{24} (ng*h/mL) (%CV)	2.60 (66.8)	5.42 (55.2)	9.01 (74.1)	18.8 (41.8)	29.2 (59.0)	43.3 (57.9)[d]	60.1 (54.7)[h]	78.9 (27.9)
Molar AP32914 to mobocertinib AUC_{24} ratio (%CV)	0.0942 (21.8)	0.0891 (39.9)	0.0930 (25.2)	0.0769 (25.0)	0.0776 (34.2)	0.0740 (44.4)[a]	0.0634 (40.2)[h]	0.0766 (24.9)
C2D1								
N	2	2	4	4	3	14	70	1
$T_{max,ss}$ (h) (range)	6.08, 7.83	1.50, 6.15	4.08 (3.93, 7.97)	7.00 (4.07, 8.08)	4.12 (4.00, 8.00)	4.10 (2.15, 7.83)	4.00 (0.00, 24.0)	3.92
$C_{max,ss}$ (ng/mL)(%CV)	0.233, 0.260	0.263, 0.427	0.772 (46.4)	1.40 (72.2)	1.97 (19.8)	3.40 (68.9)	4.96 (50.0)	5.30
$AUC_{24,ss}$ (ng*h/mL) (%CV)	3.80, 3.97	4.38, 7.85	11.1 (68.4)	22.2 (77.3)	29.3 (42.8)	51.5 (72.2)[e]	68.1 (53.5)[i]	73.3
Molar AP32914 to mobocertinib AUC_{24} ratio (%CV)	0.107, 0.114	0.0469, 0.0773	0.108 (12.0)	0.0771 (32.1)	0.0936 (33.0)	0.0684 (47.5)[e]	0.0733 (29.9)[i]	0.0978
R_{ac} for AUC_{24} (%CV)	2.03, 2.90	0.885, 1.72	1.21 (17.1)	1.29 (27.9)	1.64 (52.5)	1.23 (39.0)[f]	1.21 (53.9)[j]	1.16
Effective half-life (h) (%CV)	24.5, 39.3	19.2[a]	10.8 (34.2)[b]	9.04 (89.0)	18.3, 35.5[c]	12.0 (69.2)[g]	15.2 (59.8)[k]	8.41

%CV: percent coefficient of variation; AUC_{24}: area under the concentration-time curve from time 0 to 24 hours; $AUC_{24,ss}$: area under the concentration-time curve from time 0 to 24 hours, at steady state; C_{max}: maximum observed concentration; $C_{max,ss}$: maximum observed concentration during a dosing interval, at steady state; NSCLC: non–small-cell lung cancer; PK: pharmacokinetic; R_{ac}: accumulation ratio; t_{max}: time of first occurrence of C_{max}; $t_{max,ss}$: time of first occurrence of C_{max}, at steady state.

Parameters are presented as geometric mean (geometric %CV), except for tmax which is presented as median (range). Individual values are reported if N <3.

a N = 1; b N = 3; c N = 2; d N = 23; e N = 12; f N = 10; g N = 8; h N = 134; i N = 68; j N = 65; k N = 43.

☐: PK Parameter of the 160 mg dose at C1D1 and D2D1 highlighted by the assessor

Source: Clinical Study Report TAK-788-15-101; Table 19 pg. 115/285

- ***Accumulation***

As expressed in the accumulation ratio (Rac) values in the table above, moderate accumulation of mobocertinib systemic exposure after multiple dosing was observed in the dose range of 20 to 120 mg QD.
Mobocertinib $AUC_{24,ss}$ on Cycle 2 Day 1 following daily administration increased in a less than dose-proportional manner in the dose range of 120 mg to 160 mg as an increase in the dose by 33% resulted in a 23% increase in geometric mean steady-state mobocertinib AUC24,ss. In addition, 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).
The less than dose proportional increase in mobocertinib exposure at the higher doses and the negligible accumulation of mobocertinib exposure at the 160 mg dose suggest auto-induction of the apparent oral clearance of mobocertinib likely via induction of CYP3A.

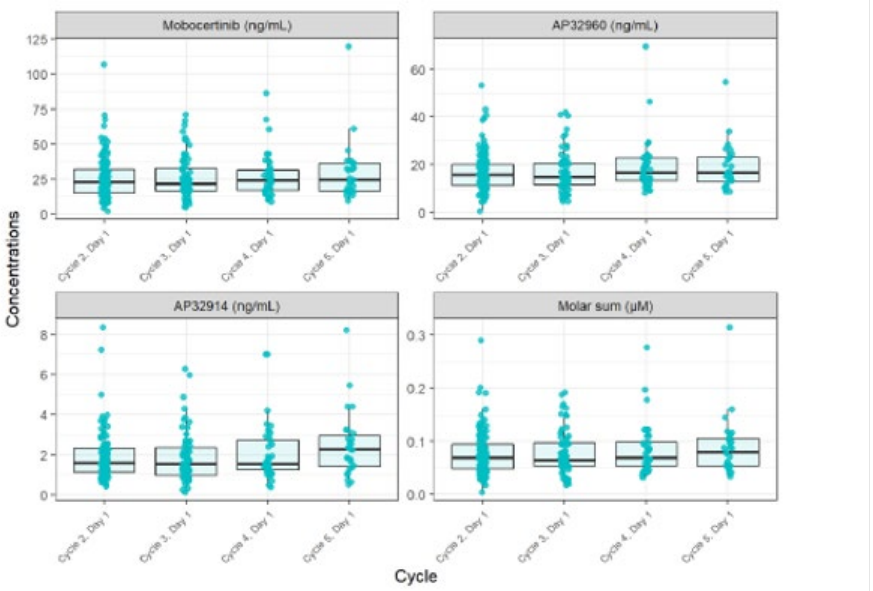
Administration of mobocertinib QD resulted in moderate accumulation of AP32960 with a geometric mean accumulation ratio of Cycle 2 Day 1 AP32960 $AUC_{24,ss}$ versus Cycle 1 Day 1 AP32960 AUC_{24} in the range of 1.34 to 1.88 across 20 mg to 160 mg mobocertinib doses.

Administration of mobocertinib QD resulted in moderate accumulation of AP32914 with a geometric mean accumulation ratio of Cycle 2 Day 1 AP32914 AUC_{24} versus Cycle 1 Day 1 AP32914 AUC_{24} in the range of 1.21 to 1.64 across the dose of 20 to 160 mg mobocertinib.

- ***Steady State***

As outlined in the elimination section of the Clinical Summary 2.7.2, based on the population PK analysis, the enzyme induction half-life following administration of mobocertinib is approximately 7.4 days, thereby supporting the achievement of steady-state systemic exposures by Cycle 2 Day 1 (Day 29 of continuous dosing). Predose concentrations of mobocertinib and its active metabolites on Day 1 of later cycles (i.e., Cycles 3, 4, and 5) were similar to those observed on Cycle 2 Day 1.

Figure pk 1. Observed predose concentrations of mobocertinib, AP32960, AP32914 and combined molar sum of mobocertinib, AP32960 and AP32914 on day 1 of Cycles 2, 3, 4, 5 in cancer patients receiving mobocertinib 160 mg QD (popPK PK analysis dataset)



PK: pharmacokinetic; QD: once daily.
Circles represent individual patient values. Box lines represent the 25th, 50th, and 75th percentiles.
Concentrations were included if the patient received 160 mg QD mobocertinib for at least 7 consecutive days before the PK sample collection.

Source: Response to D120 LoQ, question 56.

- ***BCS-class***

According to the Summary of Biopharmaceutical studies, the solubility, permeability, and dissolution characteristics of mobocertinib have been characterized according to the United States Food and Drug Administration (FDA) Biopharmaceutics Classification System (BCS) guidance and European Medicines Agency (EMA) Guideline on Investigation of Bioequivalence.

Solubility:

As the recommended dose of mobocertinib is 160 mg once daily, the solubility needs to be at least 160 mg/250 mL or 0.64 mg/mL in order for mobocertinib to be classified as highly soluble. As shown in the table below, the solubility of mobocertinib exceeded this threshold across the pH range of 1 to 6.8, thereby indicating that mobocertinib is highly soluble (all values clearly above 0.64 mg/mL):

Table pk 11. Solubility of Mobocertinib Drug Substance in the pH range of 1 to 6.8 a 37°C

Target pH	Medium	Mean Final pH	Mean Equilibrium Solubility (SD) (n = 3) (mg/mL) [a]
1	0.1 N HCl	1.03	>127 (6)
1.5	0.1 N HCl	1.51	>129 (7)
2.5	100 mM sodium phosphate	2.49	>120 (4)
3.5	100 mM sodium phosphate	3.51	30.2 (2.0)
4.5	100 mM sodium phosphate	4.52	11.2 (0.1)
6.8	100 mM sodium phosphate	6.76	>14.7 (0.6)

HCl: hydrochloric acid.

a Freebase equivalents (SD).

Source: 2.7.1 Biopharmaceutic Studies and Analytical Methods; Table 2.a pg. 24/57

Permeability

The applicant states that mobocertinib is a high permeability compound based on the *in-vitro* apparent permeability coefficient in the apical-to-basolateral direction [Papp, A-B] of 15.0 × 10^{-6} cm/sec.

The BCS classification of mobocertinib has not yet been established with respect to permeability (see non-clinical AR).

- ***Bioequivalence***
- ***Relative Bioavailability of DiC-B Compared With DiC-A***

Study TAK-788-1001 (Part 3)

Study TAK-788-1001 Part 3 compared the relative bioavailability of mobocertinib administered as DiC-B versus DiC-A in healthy subjects [*For details with regard to the study design, see section "absorption" above*].

The pharmacokinetic parameters after a single oral dose 160 mg mobocertinib DiC B (test) or 160 mg mobocertinib DiC A (reference) under fasting conditions can be summarised as follow:

Table pk 12. Statistical Assessment of Relative Bioavailability of TAK-788 DiC-B Compared to DiC-A Under Fasted Conditions

Parameter (unit)	DiC A [a] (Reference)	DiC B [a] (Test)	LS Geometric Mean Ratio (90% CI) (Test/Reference)
N	12	12	
t_{max} (h)	6.0 (2-8)	5.0 (2-8)	
C_{max} (ng/mL)	44.8 (31.5)	41.7 (27.5)	0.932 (0.846, 1.03)
AUC_{∞} (h·ng/mL)	739 (25.4)	710 (34.9)	0.960 (0.886, 1.04)
Combined molar C_{max} (nM)	130 (27.6)	121 (24.8)	0.930 (0.870, 0.995)
Combined molar AUC_{∞} (h·nM)	2190 (23.0)	2080 (30.7)	0.947 (0.886, 1.01)

AUC_{∞}: area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; DiC-A: drug-in-capsule by process A; DiC-B: drug-in-capsule by process B; PK: pharmacokinetic.
A linear mixed effect model on the natural log-transformed parameters was performed with regimen, sequence and period as a fixed effect and subject nested within sequence as a random effect. The least squares means and difference of least squares means for the log-transformed parameters were exponentiated to obtain the point estimates and 90% CIs of the geometric LS mean ratio on the original scale.

[a] Parameters are presented as geometric mean (%CV), except for tmax which is presented as median (range).

Source: Clinical Study Report TAK-788-1001; Table 11.o pg. 86/115

As outlined in the table above, 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.

- ***Relative Bioavailability of DiC-C Compared With DiC-A and DiC-B***

The intended mobocertinib commercial formulation as well as the formulation used in clinical studies is an immediate-release DiC-C formulation, in which the DS is filled directly into hard gelatin capsules, with no excipients. The available physiochemical data and clinical PK results support the achievement of similar systemic exposures after administration of mobocertinib as DiC-A, DiC-B, and DiC-C.

During the population PK analysis (described in detail in Module 2.7.2), the effect of DP on absorption parameters was formally tested and was shown to not be statistically significant and assessed by the applicant to be not clinically meaningful. Of note, the DP covariate was parameterized as DiC-C vs DiC-A/B in this analysis because bioequivalence was demonstrated between DiC-B and DiC-A in Study TAK-788-1001 Part 3, and patients in Parts 1 and 2 of Study AP32788-15-101 may have received both DiC-A and DiC-B during treatment. The distributions of the model-simulated individual combined molar area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}) of mobocertinib, AP32960, and AP32914 for DiC-A/B and DiC-C were very similar on both Cycle 1 Day 1 and Cycle 2 Day 1 for patients with cancer included in the population PK analysis. In addition, the percent change in mean combined molar AUC_{24} for DiC-C versus DiC-A/B was $\leq$1% on both Cycle 1 Day 1 and Cycle 2 Day 1.

An ANOVA was also performed on the log-transformed combined molar AUC_{24} and C_{max} data and the ratio of geometric means (and associated 90% CIs) was derived. On both Cycle 1 Day 1 and Cycle 2 Day 1, the geometric mean ratios for both parameters were close to 1, with 90% CIs that were completely contained within the 0.80 to 1.25 equivalence limits (Model-Based Relative Bioavailability Assessment Report).

- ***Influence of food***

The effect of food on mobocertinib PK was assessed in two studies. The effect of a low-fat meal was investigated in Study TAK-788-1001 (Part 2) and the effect of a high-fat meal was evaluated in Study TAK-788-1005.

- ***Effect of a low-fat meal***

<u>TAK-788-1001 (Part 2)</u>

Study TAK-788-1001 Part 2 investigated the effect of a low-fat meal on the PK of TAK-788 administered as a DiC formulation in healthy subjects [*For details with regard to the study design, see section "absorption" above*].

The pharmacokinetic parameters after single oral doses of 120 and 160 mg of mobocertinib in the fasted and fed (low-fat meal) state can be summarised as follow:

Table pk 13. Assessment of the Effect of a Low-Fat Meal on Mobocertinib PK

Dose	Parameter (unit)	Fasted [a] (Reference)	Low-fat meal [a] (Test)	LS Geometric Mean Ratio (90% CI) (Test/Reference)
120 mg	N	6	6	
	t_{max} (h)	4.00 (2.00-6.00)	6.00 (4.00-8.00)	
	C_{max} (ng/mL)	31.2 (47.0)	27.5 (38.7)	0.881 (0.711-1.09)
	AUC_{∞} (h·ng/mL)	526 (51.4)	534 (47.1)	1.02 (0.898-1.15)
	Combined molar C_{max} (nM)	88.0 (41.1)	77.3 (31.0)	0.878 (0.721-1.07)
	Combined molar AUC_{∞} (h·nM)	1520 (42.3)	1530 (38.0)	1.01 (0.904-1.12)
160 mg	N	10	10	
	t_{max} (h)	6.00 (2.00-12.0)	6.00 (2.00-8.00)	
	C_{max} (ng/mL)	41.0 (47.9)	39.5 (40.0)	0.964 (0.836-1.11)
	AUC_{∞} (h·ng/mL)	743 (53.6)	706 (38.4)	0.951 (0.874-1.03)
	Combined molar C_{max} (nM)	119 (40.8)	113 (33.1)	0.948 (0.835-1.08)
	Combined molar AUC_{∞} (h·nM)	2320 (45.0)	2110 (32.7)	0.943 (0.867-1.03)

%CV: percent coefficient of variation; AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinity; Cmax: maximum observed plasma concentration; LS: least squares; PK: pharmacokinetic; tmax: time of first occurrence of Cmax.

A linear mixed-effect model on the natural log-transformed parameters was performed with treatment regimen, sequence, and period as a fixed effect and subject nested within sequence as a random effect. The LS means and difference of LS means for the log-transformed parameters were exponentiated to obtain the point estimates and

90% CIs of the geometric LS mean ratio on the original scale.

a Parameters are presented as geometric mean (%CV), except for tmax which is presented as median (range).

Source: 2.7.1 Biopharmaceutic Studies and Analytical Methods; Table 2.d pg. 35/57

For the exploratory assessment of the 120 mg dose, the mobocertinib median time of first occurrence of C_{max} (t_{max}) was 4 hours post dose under fasted conditions and 6 hours post dose after a low-fat meal. The geometric mean ratios of mobocertinib C_{max} and the combined molar C_{max} of mobocertinib, AP32960, and AP32914 [*data not shown, see CSR*] decreased 11.9% and 12.2%, respectively, while mobocertinib AUC_{∞} and the combined molar AUC_{∞} of mobocertinib, AP32960, and AP32914 [*data not shown, see CSR*] increased 2% and 1%, respectively, when comparing low-fat meal administration with fasted conditions. The 90% CI for mobocertinib AUC_{∞} and the combined molar AUC_{∞} fell completely within the 80% to 125% equivalence limits, indicating that a low-fat meal had no clinically meaningful effect on the AUC_{∞} of mobocertinib and the combined molar AUC_{∞} of mobocertinib, AP32960, and AP32914. The lower bound of the 90% CI for both mobocertinib C_{max} and the combined molar C_{max} was slightly below the lower bound of the equivalence limits, which likely reflects the small sample size at the 120 mg dose (n = 6). However, because total systemic exposure (ie, combined molar AUC) was within the equivalence limits, the slightly lower C_{max} is not considered to be clinically relevant.

At the 160 mg dose, the median t_{max} of mobocertinib was 6 hours post dose after administration with or without a low-fat meal. The geometric mean ratios for mobocertinib C_{max} and AUC_{∞}, as well as the combined molar C_{max} and AUC_{∞} of mobocertinib, AP32960, and AP32914 [data not shown, see CSR] were close to 1 when comparing the exposures with a low-fat meal with those under fasted conditions. The 90% CI for all 4 PK parameters was contained completely within the 80% to 125% equivalence limits.

- ***Effect of a high-fat meal***

TAK-788-1005:

Study title	A Phase 1, Randomized, 2-Period, 2-Sequence, Crossover Study to Evaluate the Effect of High-Fat Meal on TAK-788 Pharmacokinetics in Healthy Adult Subjects
Study design	This was an open-label, randomized, 2-period, and 2-sequence crossover high-fat meal effect study in healthy adult subjects. A total of 14 subjects were randomized in a 1:1 ratio and received a single oral dose of 160 mg mobocertinib (commercial formulation; DiC-C size 2) under fasted conditions or after consumption of a high-fat meal on Day 1 of Period 1, and again under the alternative food intake condition on Day 1 of Period 2. The high-fat meal contained 800 to 1000 total calories, including 500 to 600 calories, 55 to 65 g fat, or 50% from fat. PK samples were collected at prespecified times up to 240 hours post dose.
Study objectives	*Primary objectives* To characterize the effect of a high-fat meal on the pharmacokinetics (PK) of mobocertinib administered as a proposed commercial product. *Secondary objectives* To assess the PK of active metabolites AP32960 and AP32914 of mobocertinib. *Additional Objectives:* To collect the safety data of mobocertinib following a single oral dose in healthy adult subjects.
Study period	Date first subject signed informed consent form: 22 June 2020 Date of last subject's last visit/contact: 11 August 2020 Date of last dose of study drug: 11 July 2020
No. of subjects	Thirty-one (31) subjects were screened and a total of 14 subjects entered and completed the study.
Treatment	Subjects received the following treatments on one occasion in a crossover fashion to evaluate the effect of a high-fat meal Treatment A: Administration of a single oral dose of 160 mg mobocertinib (4 x 40 mg capsules) following an overnight fast (reference). Treatment B: Administration of a single oral dose of 160 mg mobocertinib (4 x 40 mg capsules) with a high-fat meal[1] (test).

Results

The pharmacokinetic parameters after single oral doses of 160 mg of mobocertinib in the fasted and fed state (high-fat meal) can be summarised as follows:

[1] * 800-1000 total calories, 500-600 calories, 55-65 g, or 50% from fat

Table pk 14. Assessment of the Effect of a High-Fat Meal on Mobocertinib PK

Dose	Parameter (unit)	Fasted [a] (Reference)	High-fat meal [a] (Test)	Geometric LS Mean Ratio (90% CI) (Test/Reference)
160 mg	N	13	14	
	t_{max} (h)	6.01 (4.00-8.00)	8.00 (4.01-12.0)	---
	C_{max} (ng/mL)	56.8 (47.1)	56.6 (40.9)	1.02 (0.960-1.09)
	AUC_{∞} (h·ng/mL)	1030 (61.1)	1230 (59.5)	1.22 (1.14-1.31)
	Combined molar C_{max} (nM)	161 (34.2)	153 (31.0)	0.970 (0.910-1.05)
	Combined molar AUC_{∞} (h·nM)	3290 (46.4) [b]	3870 (50.7)[c]	1.13 (1.07-1.20)

AUC∞: area under the concentration-time curve from time 0 to infinity; Cmax: maximum observed plasma concentration; CV: coefficient of variation; LS: least squares; PK: pharmacokinetic; tmax: time of first occurrence of Cmax.

A linear mixed-effect model on the natural log-transformed parameters was performed with treatment regimen, sequence- and period as a fixed effect and subject nested within sequence as a random effect. The LS means and difference of LS means for the log-transformed parameters were exponentiated to obtain the point estimates and

90% CIs of the geometric LS mean ratio on the original scale.

a Parameters are presented as geometric mean (%CV), except for tmax, which is presented as median (range).

b N = 12.

c N = 11.

Source: 2.7.1 Biopharmaceutic Studies and Analytical Methods; Table 2.g pg. 43/57

As outlined in the table above, the mobocertinib median t_{max} was 6.01 hours post dose under fasted conditions and 8 hours post dose after a high-fat meal.

The geometric mean ratios of mobocertinib C_{max} and the combined molar C_{max} of mobocertinib, AP32960, and AP32914 [*data not shown, see CSR*] after high-fat meal administration compared to fasted conditions were close to 1 with 90% CIs that were contained within the 80% to 125% equivalence limits.

The AUC_{∞} of mobocertinib and the combined molar AUC_{∞} of mobocertinib, AP32960, and AP32914 [*data not shown, see CSR*] were approximately 22%, and 13% higher, respectively, following administration of 160 mg mobocertinib with a high-fat meal compared to fasted conditions.

However, the 90% CI for the geometric mean ratio for combined molar AUC_{∞} was contained within the 80% to 125% equivalence limits, thereby indicating that a high-fat meal has no clinically meaningful effect on combined molar systemic exposures.

Distribution

Mobocertinib and its metabolites AP32960 and AP32914 were found to be 99.3%, 99.5%, and 98.6% bound to human plasma proteins, respectively, *in vitro* at concentrations ranging from 0.5 to 5.0 µM. No apparent concentration-dependent trends were observed. These findings indicate that mobocertinib and its 2 active metabolites are highly bound to human plasma proteins.

The applicant stated that samples are being collected in the ongoing studies Study TAK-788-1007 and Study TAK-788-1008 to measure the plasma protein binding of mobocertinib and its metabolites in subjects with organ impairment and matched healthy subjects with normal organ function. Data from Study TAK-788-1007 and Study TAK-788-1008 are not available at the time of this submission.

An *in vitro* study showed that the blood-to-plasma partition ratios for mobocertinib and AP32960 were nearly constant across the concentration range (0.1 to 5 µM) tested. Mean blood-to-plasma ratios for mobocertinib and AP32960 in human blood were 0.95 and 1.01, respectively (Non-Clinical Module 2.6.4

Section 4.3). These findings indicate that mobocertinib and AP32960, at nominal concentrations of 0.1 to 5 µM, did not show preferential distribution into red blood cells (RBCs) over plasma. The blood-to-plasma ratio for AP32914 has not been determined *in vitro*.

In addition, mobocertinib, AP32960, and AP32914 did not show preferential distribution into human whole blood over plasma based on data from the human ADME study (Study TAK-788-1002 Period 2).

The geometric mean apparent volume of distribution at steady-state for mobocertinib is estimated to be 3510 L (90% CI: 3410, 3610 L) based on the population PK model.

Elimination

TAK-788-1001 (see section 2.1.3 "Absorption" for details regarding study design)

Half-life, clearance, volume of distribution

The geometric mean terminal $t_{1/2z}$ ranged from 14.3 to 19.9 hours across the 20 to 160 mg dose range. Geometric mean CL/F and V_z/F values of TAK-788 ranged from 157 to 314 L/h and 4500 to 8190 L, respectively. There were no apparent dose-related trends in $t_{1/2z}$, CL/F or V_z/F.

Excretion

TAK-788-1001 (see section 2.1.3 "Absorption" for details regarding study design)

Urine PK Results

Study TAK-788-1001 Part 1 also investigated urine PK [*For details with regard to the study design, see section "absorption" above*]. Descriptive statistics of TAK-788 urine PK parameters following single oral administration of TAK-788 at 20, 40, 80, 120, and 160 mg are provided in the table below:

Table pk 15. Summary of Urine TAK-788 PK Parameters Following Single Oral Dose Administration of TAK-788 to Healthy Subjects

PK Parameter (unit)	TAK-788 20 mg	TAK-788 40 mg	TAK-788 80 mg	TAK-788 120 mg	TAK-788 160 mg
N	6	6	6	6	6
Ae_{48} (mg)	0.174 (38.1)	0.439 (66.2)	0.509 (57.2)	0.757 (50.7)	1.86 (82.4)
CL_R (mL/h)	3250 (47.3)	3100 (14.0)	2160 (47.6)	1860 (80.0)	2110 (39.2)
$f_{e,t}$ (%)	0.870 (37.9)	1.10 (66.3)	0.636 (57.0)	0.632 (50.8)	1.16 (82.4)

Ae_{48}: amount of drug excreted in urine from time 0 to 48 hours post-dose; CL_R: renal clearance; $f_{e,t}$: fraction of administered dose of drug excreted in urine from time 0 to the last collection time.

Parameters are presented as geometric mean (%CV).

Source: Clinical Study Report TAK-788-1001; Table 11.i pg. 73/115

Within 48 hours after single oral dose administration of TAK-788, approximately 0.632% to 1.16% of the administered TAK-788 was excreted unchanged in urine across all dose groups. Geometric mean CL_R values for TAK-788 ranged from 1860 to 3250 mL/h which was lower than the average glomerular filtration rate (7200 mL/h).

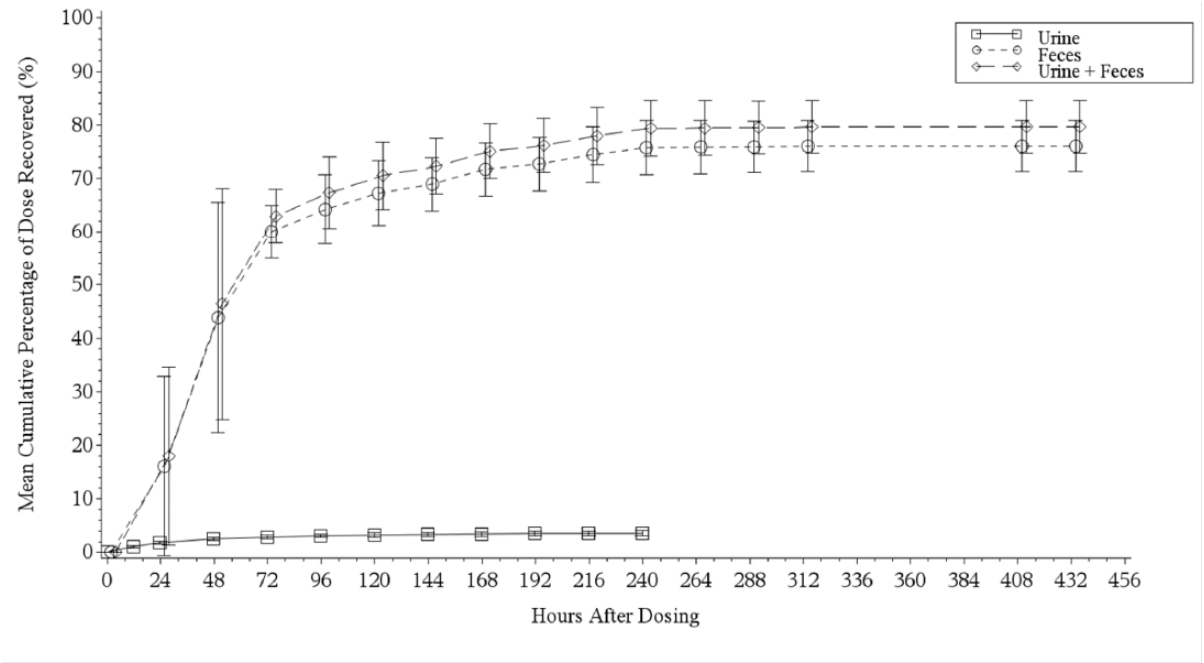
In Study TAK-788-1001, the renal clearance of mobocertinib following a 160 mg single dose was 2110 mL/h (2.11 L/hr). This value is approximately 1.95% of the CL/F estimate from the population PK analysis.

TAK-788-1002 (see section 2.1.3 "Absorption" for details regarding study design)

Urine and feces PK Results

Arithmetic mean (SD) urine, feces, and combined urine and feces Cum%Dose recovered versus time profiles of total radioactivity following a single oral dose of 160 mg (~100 µCi) [^{14}C]-mobocertinib in healthy male subjects are presented in the figure below:

Figure pk 2. Arithmetic Mean (SD) Urine, Feces, and Combined Urine and Feces Cumulative Percentage of Dose Recovered Versus Time Profiles of Total Radioactivity Following Administration of a Single Oral Dose of 160 mg (~100 µCi) [14C]-TAK-788 in Healthy Male Subjects (Period 2)



Feces and Urine + Feces are shifted to the right for ease of reading

Source: Clinical Study Report TAK-788-1002; Fig 11.d pg. 94/113

Individual subject results and a summary of the percentage of the radioactive dose recovered in urine, feces, and urine and feces combined for the entire sampling duration following a single oral dose of 160 mg (~100 µCi) [^{14}C]-mobocertinib in healthy male subjects are presented in the table below:

Table pk 16. Individual Subject Results and Summary of Percentage of Radioactive Dose Recovered in Urine, Feces, and Urine and Feces Combined Following Administration of a Single Oral Dose of 160 mg (~100 µCi) [^{14}C]-TAK-788 in Healthy Male Subjects (Period 2)

Pharmacokinetic Parameter	Subject 1001	Subject 1002	Subject 1003	Subject 1004	Subject 1006	Subject 1105	Geometric Mean (Geometric CV%)
Urine							
Cum%Dose (%)	3.12	4.44	3.73	3.57	3.45	3.23	3.57 (12.6) [n=6]
Feces							
Cum%Dose (%)	79.8	77.7	75.7	76.7	79.8	67.0	76.0 (6.50) [n=6]
Urine + Feces							
CombCum%Dose (%)	83.0	82.1	79.5	80.3	83.2	70.2	79.6 (6.40) [n=6]

The values for Cum%Dose in urine and feces and CombCum%Dose in urine and feces combined are for the entire duration of sample collection.

Source: Clinical Study Report TAK-788-1002; Tab 11.n pg. 94/113

The Cum%Dose of radioactivity recovered in the urine of individual subjects ranged from 3.12% to 4.44%, and the Geom Mean recovery in urine was 3.57%. The Cum%Dose of radioactivity recovered in the feces of individual subjects ranged from 67.0% to 79.8%, and the Geom Mean recovery in feces was 76.0%. The Cum%Dose of radioactivity recovered in both excreta combined for the individual subjects ranged from 70.2% to 83.2%, and the Geom Mean recovery in both excreta combined was 79.6%.

A summary of urine mobocertinib, AP32960, and AP32914 PK for the entire sampling duration following a single oral dose of 160 mg (~100 µCi) [^{14}C]-mobocertinib in healthy male subjects is presented in Table below:

Table pk 17. Summary of Urine TAK-788, AP32960, and AP32914 Pharmacokinetics Following Administration of a Single Oral Dose of 160 mg (~100 µCi) [^{14}C]-TAK-788 in Healthy Male Subjects (Period 2)

Pharmacokinetic Parameter	TAK-788 N=6	AP32960 N=6	AP32914 N=6
CumAe (mg)	0.627 (31.1)	0.949 (16.3)	0.213 (23.5)
Cum%Dose (%)	0.387 (31.3)	0.600 (16.3)	0.135 (23.1)
CL_R (L/hr)	0.657 (44.3)	1.95 (22.5)	2.85 (27.9)

The values for CumAe and Cum%Dose are for the entire duration of sample collection. Parameter values are presented as geometric mean (geometric percent coefficient of variation).

Source: Clinical Study Report TAK-788-1002; Tab 11.o pg. 95/113

In Study TAK-788-1002 Period 2, the geometric mean renal clearance for mobocertinib was 0.657 L/hr (see table above), which is approximately 0.608% of the CL/F from the population PK analysis and is consistent with the results observed in Study TAK-788-1001.

A summary of urine PK of mobocertinib, AP32960, and AP32914 combined for the entire sampling duration following a single oral dose of 160 mg (~100 µCi) [^{14}C]-mobocertinib in healthy male subjects is presented in Table below:

Table pk 18. Summary of Urine Pharmacokinetics of TAK-788, AP32960, and AP32914 Combined Following Administration of a Single Oral Dose of 160 mg (~100 µCi) [^{14}C]-TAK-788 in Healthy Male Subjects (Period 2)

Pharmacokinetic Parameter	TAK-788, AP32960, and AP32914 Combined N=6
Combined Molar CumAe (nmol)	3120 (19.7)
Combined Cum%Dose (%)	1.13 (19.7)
Combined CL_R (L/hr)	1.22 (30.6)

Parameter values are presented as geometric mean (geometric percent coefficient of variation).

Source: Clinical Study Report TAK-788-1002; Tab 11.p pg. 95/113

These results indicate that 0.387%, 0.600%, and 0.135% of the oral dose of [^{14}C]-mobocertinib was recovered in the urine as mobocertinib, AP32960, and AP32914, respectively, for a total of 1.13% of the dose being recovered as all 3 analytes combined. This is less than the overall recovery of the dose in urine of 3.57%.

The Geom Mean CL_R of all 3 analytes in urine was low, ranging from 0.657 to 2.85 L/hr, resulting in a Combined CL_R for all 3 analytes of only 1.22 L/hr.

Metabolism

As outlined by the applicant in the Clinical Summary, metabolism appears to be the major mechanism of mobocertinib clearance. Using rhCYPs in *in vitro* investigations, 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.

TAK-788-1002 (see section 2.1.3 "Absorption" for details regarding study design)

Metabolism

The human ADME properties of mobocertinib were evaluated after administration of radiolabeled [^{14}C]-mobocertinib (Study TAK-788-1002 Period 2).

The metabolic profiles of [^{14}C]-mobocertinib in human excreta (urine and feces) after oral administration of 160 mg (100 µCi) were evaluated using high performance liquid chromatography coupled to traditional radiometric analysis. Metabolite identification and structure elucidation were carried out by high performance liquid chromatography high-resolution mass spectrometry analysis (Report TKD-BCS-00362-R1).

Plasma metabolites

In plasma, mobocertinib was the most abundant extracted circulating component and accounted for 7.65% of total extracted circulating radioactivity. Metabolites M108, M70, M107, M106, and M67 (AP32960) accounted for 7.14%, 6.76%, 5.94%, 5.30%, and 5.17% of total extracted circulating radioactivity, respectively. The remaining radioactivity was distributed into many minor circulating components each with <4% of the total extracted circulating radioactivity. There was no single metabolite accounting for >10% of the total extracted circulating radioactivity.

Urinary metabolites

Five metabolites (M53, M66, M67 [AP32960], M69, and M70) were detected in urine and each contributed to less than 0.9% of the dose (ranging from 0.3% to 0.8% of the dose).

Faecal metabolites

In the feces, metabolite M67 [AP32960] was the most abundant metabolite and represented approximately 12% of the dose. In addition, 12 metabolites (M35, M42, M44, M46, M53, M55, M60, M63, M66, M68, M70, and M71), all derived from oxidation of mobocertinib except for M70, were identified and ranged from approximately 2% to 6% of the dose. A number of unidentified minor metabolites as radioactive peaks together contributed to approximately 12% of the dose, and each of these metabolites was less than 3% of the dose. Therefore, the majority of the metabolites identified were derived from the oxidation of mobocertinib, accounting for 46% of the dose, with a minor contribution of 4% of the dose undergoing direct conjugation.

Summary:

Table pk 19. Percent of the Dose for TAK-788 and Its Metabolites in Excreta of Healthy Subjects Administered an Oral Dose of [^{14}C] TAK-788

	% of the Dose		
Analyte	Urine	Feces	Total
TAK-788:	0.9	5.9	6.8
Sum of Identified Metabolites:	2.1	47.7	49.8
Sum of Unidentified Metabolites:	0.3	11.8	12.1
Total:	3.3	65.4	68.7

Parameter values are presented as geometric mean (geometric percent coefficient of variation).

Source: TKD-BCS-00362-R1; Tab 4 pg. 25/58

A summary of excretion of TAK-788 and its metabolites in urine and feces is presented in the Table pk 19 above. Thereafter, approximately 7% of the dose accounted for TAK-788 in excreta, approximately 50% of the dose contributed to the identified metabolites and 12% of the dose represented the sum of unidentified metabolites.
Thus, a total of 61.9% (49.8% + 12.1%) of the dose accounted for the metabolites of TAK-788.
A total of percentage of the dose identified is 56.6% (6.8% + 49.8%). Therefore, approximately 80% (79.7% = 56.6/71.0*100%) of the dose processed (71.0% in table below) for metabolite profiling is characterized. Both renal and hepatic excretion of TAK-788 is minimal (approximately 1% and 6% of the dose, respectively).

In Period 2 of this study, where 6 healthy male subjects were dosed with 160 mg [^{14}C]-mobocertinib, mobocertinib accounted for 5.9% (arithmetic mean) of the dose in feces.
The arithmetic mean total radioactivity recovery from urine and feces was 79.7% of the dose, and the percentage of the dose processed for metabolite profiling was 71.0% of the dose administered (arithmetic mean).
The total fractional absorption of the mobocertinib dose is therefore 91.7% = {[(71.0 – 5.9)/71.0]*100} if normalized to the administered dose.

Table pk 20. Estimation of Absorption Fraction of TAK-788 Following an Oral Dose of [^{14}C] TAK-788 Administered to Healthy Subjects

Matrix	Mean % of the Dose Recovered	Mean % of Recovered Dose Pooled for Processing	Mean % of the Dose Processed	Fraction of the Dose Absorbed (%)
Urine	3.59	92.2	3.31	
Feces	76.1	89.0	67.7	91.7 [a]
Total	79.7	NA	71.0	

NA: not applicable.

a Fraction of the dose absorbed = (71.0 - 5.9)/71.0 × 100%.

Source: TKD-BCS-00362-R1; Tab 4 pg. 26/58

In vivo absorption greater than 85% of dose is consistent with a Biopharmaceutics Classification System (BCS) class 1 drug. This calculation assumes that there is no metabolism or degradation of unabsorbed mobocertinib in the lumen of the GI tract.
To confirm this assumption, [^{14}C]-mobocertinib was incubated in human feces for 24 hours and no metabolism or degradation products were detected in the radiochromatograms. Additionally, studies performed during development to evaluate GI stability indicated that no more than 1% of the main degradation product is expected to form in the stomach or duodenum over 2 hours. The BCS classification of mobocertinib has, however, not yet been established.

The oral absorption of TAK-788 is estimated to be approximately 92% (combined data from urine and feces).
The primary clearance route for TAK-788 in human subjects following a PO dose of [^{14}C] TAK-788 is via oxidative transformation as most of the identified drug-related materials were oxidative metabolites. As a high proportion of radioactivity in plasma was covalently, and apparently irreversibly, bound, this can also be considered an elimination pathway for mobocertinib and metabolites.

Dose proportionality and time dependencies

Dose proportionality

Dose proportionality of TAK-788 AUC_{∞} and combined molar AUC_{∞} of TAK-788, AP32960, and AP32914 after single oral dose oral administration of TAK-788 was evaluated in the dose range of 40 to 160 mg via a power model using pooled exposure data from all 3 parts of the study. Given that the low-fat meal does not impact the PK of TAK-788 and bioavailability of DiC B is similar to that of DiC A, the exposure data from all parts of the study were pooled in this dose proportionality analysis. A total of 80 TAK-788 AUC_{∞} and 74 combined molar AUC_{∞} values were included in this analysis.

The calculated slopes (95% CIs) of the linear regression line using log-transformed data were 1.20 (0.928‑1.46) for the relationship between TAK-788 AUC_{∞} and dose and 1.14 (0.835-1.44) for the relationship between the combined molar AUC_{∞} and dose. The 95% CIs of Coefficients for both PK parameters contained 1, implying approximate dose proportionality in the dose range of 40 to 160 mg TAK-788.

Dose proportionality was also tested with the exposure data from the single rising dose (SRD) study (Part 1) in the dose ranges of 20 to 160 mg, 40 to 160 mg and 80 to 160 mg only [*data not shown, see CSR table 15.2.4*]. The results of dose proportionality analysis using the AUC_{∞} estimated in the SRD Part 1 study were similar to this pooled data analysis but the 90% CIs were wider using the limited data from Part 1 only.

Time dependencies

As outlined in the absorption section above, mobocertinib $AUC_{24,ss}$ on Cycle 2 Day 1 following daily administration increased in a less than dose-proportional manner in the dose range of 120 mg to 160 mg as an increase in the dose by 33% resulted in a 23% increase in geometric mean steady-state mobocertinib AUC24,ss. In addition, 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). The less than dose proportional increase in mobocertinib exposure at the higher doses and the negligible accumulation of mobocertinib exposure at the 160 mg dose was discussed to suggest auto-induction of the apparent oral clearance of mobocertinib likely via induction of CYP3A.

In a sensitivity analysis for dose-proportionality following multiple doses across the 20 mg to 160 mg dose range (PK data were available from ≥3 patients over this dose range on Cycle 2 Day 1), the slope coefficients (90%CI) for combined molar AUC24 and Cmax were 1.02 (0.85, 1.19) and 1.06 (0.898, 1.23), respectively.

The applicant investigated CYP3A4/5 activity by measurements of 4β-hydroxycholesterol and cholesterol. The 160 mg mobocertinib QD in the dose expansion cohorts (Part 2) was the only dose level where 4β-hydroxycholesterol and cholesterol were evaluated. Patients with dose reduction and dose interruption in Cycle 1 were excluded from summary statistics using the criteria defined in the CSR. Administration of 160 mg mobocertinib QD resulted in a decrease of approximately 23% in plasma 4β-hydroxycholesterol concentration and an increase of approximately 6% in the ratio of 4β-hydroxycholesterol to cholesterol on Cycle 2 Day 1 compared to the baseline ratio.

Special populations

The effect of intrinsic factors including age, sex, body weight, race, mild-to-moderate renal impairment, and mild hepatic impairment were assessed in the population PK analysis.

Two clinical studies are currently ongoing in subjects with severe renal impairment (Study TAK-788-1007) and in subjects with moderate or severe hepatic impairment (Study TAK-788-1008) to further evaluate the effect of organ impairment on the PK of mobocertinib and its 2 active metabolites.

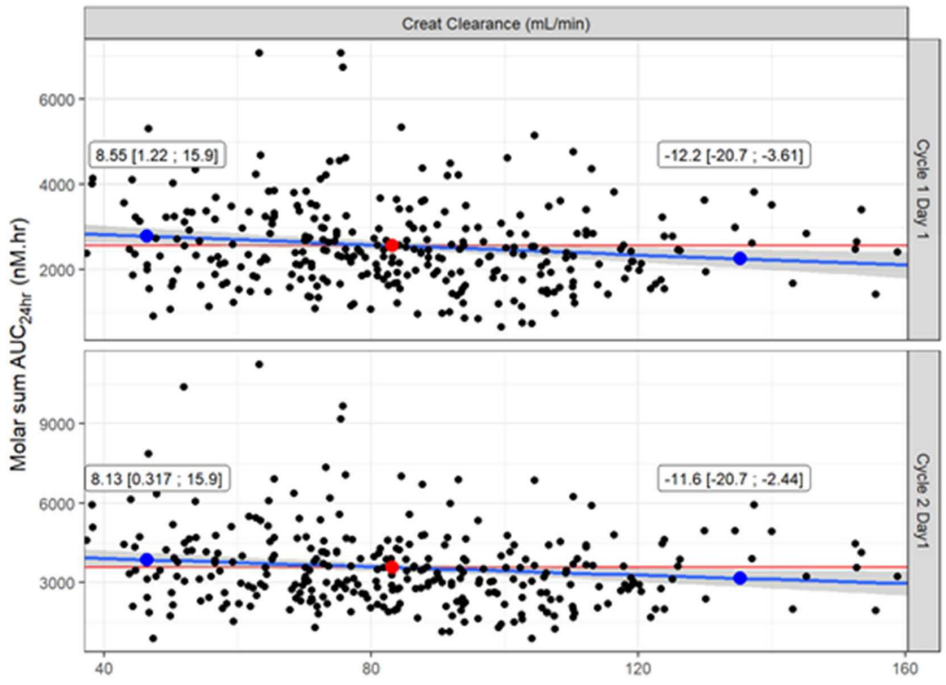
- ***Impaired renal function***

Patients with mild or moderate renal impairment have been included in clinical studies conducted during the development of mobocertinib.

In the population PK analysis, CrCL (26.3 to 251 mL/min) and eGFR (33.6 to 304 mL/min/1.73 m^2) were not identified as significant covariates, indicating that the PK of mobocertinib and its active metabolites is similar in patients with normal renal function, mild renal impairment (137 patients in popPK data set), or moderate renal impairment (ie, CrCL ≥30 mL/min; eGFR ≥30 mL/min/1.73 m^2, 24 patients in popPK data set).

Additionally, individual predicted combined molar exposures of mobocertinib, AP32960, and AP32914 following administration of mobocertinib 160 mg QD to patients with NSCLC were calculated on Cycle 1 Day 1 and Cycle 2 Day 1 using the final model and are presented versus CrCL and versus eGFR in the figures below below.

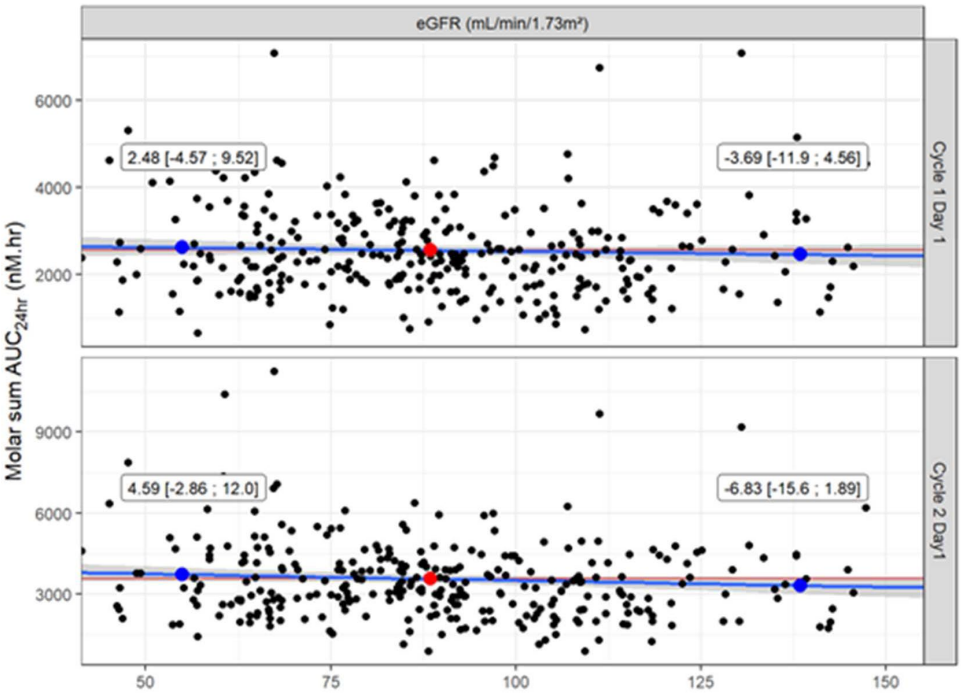
Figure pk 4. Individual Predicted Combined Molar AUC_{24} of Mobocertinib, AP32960, and AP32914 Versus Creatinine Clearance for Patients with NSCLC



Red and blue circles indicate the median and 5th and 95th percentiles of individual covariate values, respectively. Black circles represent individual predicted values. Numbers (brackets) show the percent change in m ean combined molar AUC24hr at the 5th and 95th percentile relative to the value at the median, based on the linear regression (and 95% CI). The blue line is a linear regression and the gray shaded area the associated 95% CI. The red horizontal line represents combined molar AUC_{24hr} at the median value for the covariate. Plots display the 2.5-97.5 percentile range of the covariate.
AUC_{24hr}: area under the plasma concentration-time curve from time 0 to 24 hours; CI: confidence interval; NSCLC: non-small cell lung cancer.

Source: 2.7.2 Clinical Pharmacology Studies; Figure 3.f pg. 108/179

Figure pk 5. Individual Predicted Combined Molar AUC24 of Mobocertinib, AP32960, and AP32914 Versus Estimated Glomerular Filtration Rate for Patients with NSCLC



Red and blue circles indicate the median and 5th and 95th percentiles of individual covariate values, respectively. Black circles represent individual predicted values. Numbers (brackets) show the percent change in m ean combined molar AUC24hr at the 5th and 95th percentile relative to the value at the median, based on the linear regression (and 95% CI). The blue line is a linear regression and the gray shaded area the associated 95% CI. The red horizontal line represents combined molar AUC_{24hr} at the median value for the covariate. Plots display the 2.5-97.5 percentile range of the covariate.
AUC_{24hr}: area under the plasma concentration-time curve from time 0 to 24 hours; CI: confidence interval; NSCLC: non-small cell lung cancer.

Source: 2.7.2 Clinical Pharmacology Studies; Figure 3.g pg. 109/179

The magnitudes of percent difference in combined molar AUC_{24} at the 5th or 95th percentiles of CrCL or eGFR relative to the median combined molar AUC_{24} were <15% on both Cycle 1 Day 1 and Cycle 2 Day 1.
According to the applicant, these findings are consistent with a lack of a clinically meaningful effect of CrCL or eGFR on mobocertinib PK and it is concluded that no dose adjustment is required for patients with mild or moderate renal impairment.

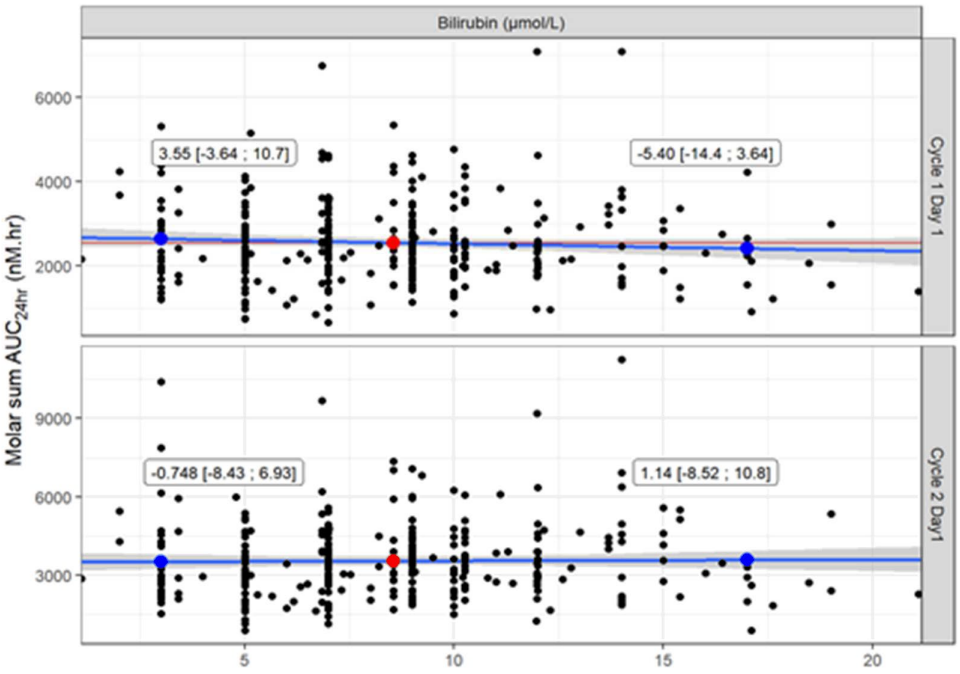
A clinical study is currently ongoing in subjects with severe renal impairment (Study TAK-788-1007) to further evaluate the effect of organ impairment on the PK of mobocertinib and its 2 active metabolites.

- ***Impaired hepatic function***

During clinical development, patients were allowed to enroll in clinical studies if their total bilirubin was ≤1.5 times the ULN and their AST and ALT were ≤2.5 times the ULN. Accordingly, patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG, 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. The popPK data set included 54 patients with mild hepatic impairment, while the remaining patients had normal hepatic function.

Bilirubin, ALT, and AST were not identified as statistically significant covariates in the population PK analysis. Individual predicted combined molar exposures of mobocertinib, AP32960, and AP32914 following administration of mobocertinib 160 mg QD to patients with NSCLC were calculated on Cycle 1 Day 1 and Cycle 2 Day 1 using the final model and are presented versus bilirubin, ALT and AST in the figures below.

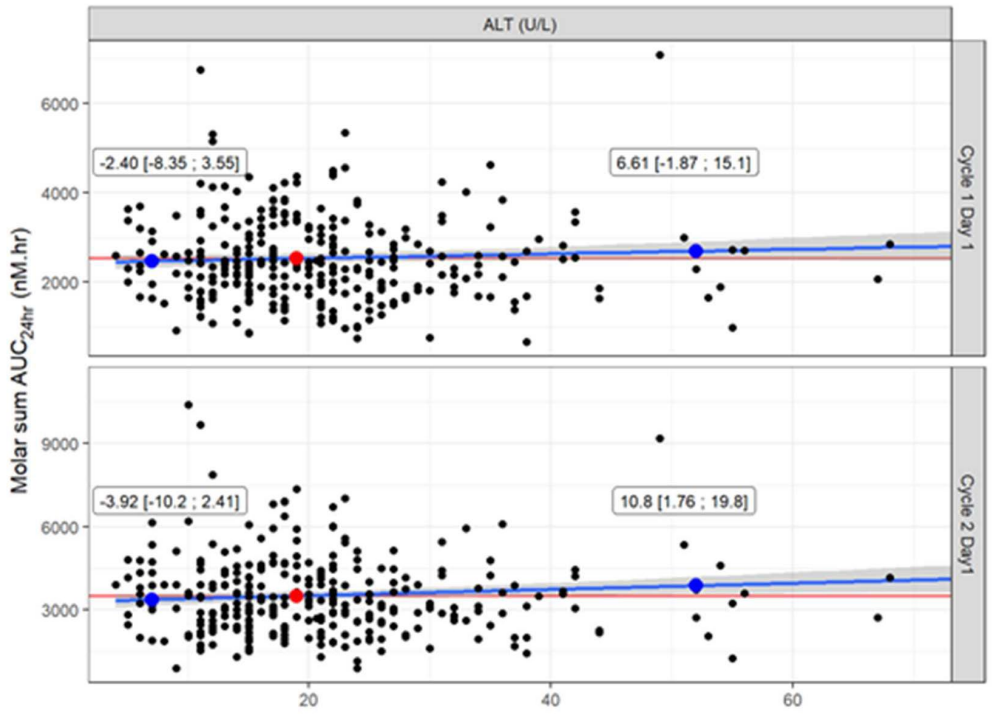
Figure pk 6. Individual Predicted Combined Molar AUC_{24} of Mobocertinib, AP32960, and AP32914 Versus Bilirubin in Patients with NSCLC



Red and blue circles indicate the median and 5th and 95th percentiles of individual covariate values, respectively. Black circles represent individual predicted values. Numbers (brackets) show the percent change in m ean combined molar AUC24hr at the 5th and 95th percentile relative to the value at the median, based on the linear regression (and 95% CI). The blue line is a linear regression and the gray shaded area the associated 95% CI. The red horizontal line represents combined molar AUC_{24hr} at the median value for the covariate. Plots display the 2.5-97.5 percentile range of the covariate.
AUC_{24hr}: area under the plasma concentration-time curve from time 0 to 24 hours; CI: confidence interval; NSCLC: non-small cell lung cancer.

Source: 2.7.2 Clinical Pharmacology Studies; Figure 3.h pg. 111/179

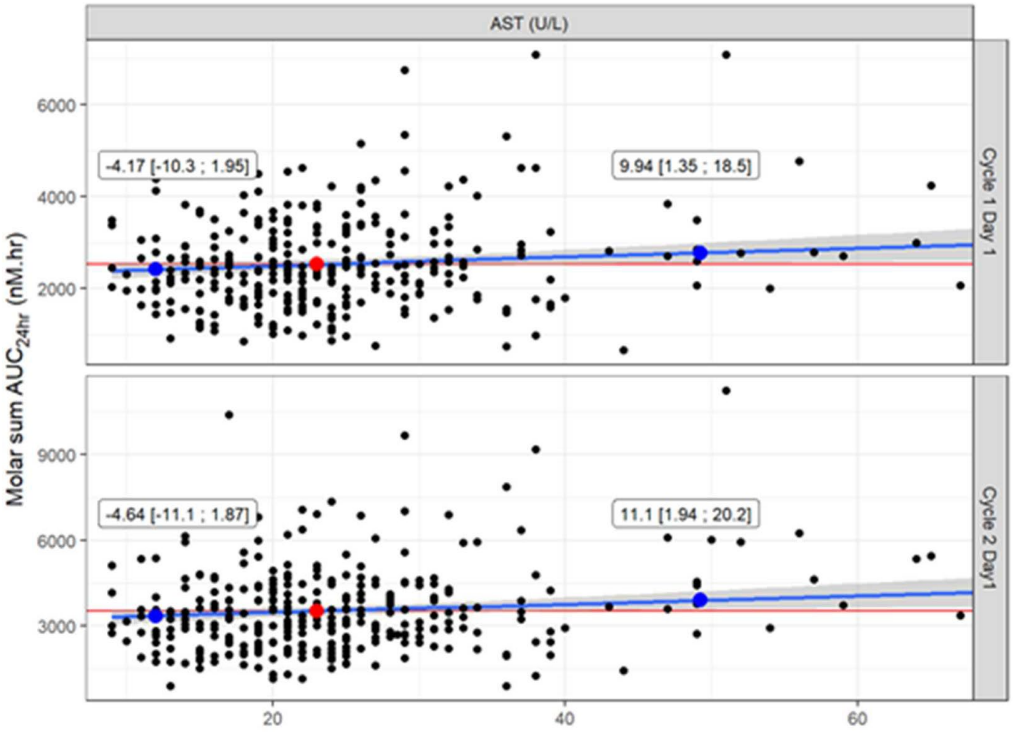
Figure pk 7. Individual Predicted Combined Molar AUC24 of Mobocertinib, AP32960, and AP32914 Versus ALT in Patients with NSCLC



Red and blue circles indicate the median and 5th and 95th percentiles of individual covariate values, respectively. Black circles represent individual predicted values. Numbers (brackets) show the percent change in m ean combined molar AUC24hr at the 5th and 95th percentile relative to the value at the median, based on the linear regression (and 95% CI). The blue line is a linear regression and the gray shaded area the associated 95% CI. The red horizontal line represents combined molar AUC_{24hr} at the median value for the covariate. Plots display the 2.5-97.5 percentile range of the covariate.
AUC_{24hr}: area under the plasma concentration-time curve from time 0 to 24 hours; CI: confidence interval; NSCLC: non-small cell lung cancer.

Source: 2.7.2 Clinical Pharmacology Studies; Figure 3.i pg. 112/179

Figure pk 8. Individual Predicted Combined Molar AUC24 of Mobocertinib, AP32960, and AP32914 Versus AST in Patients with NSCLC



Red and blue circles indicate the median and 5th and 95th percentiles of individual covariate values, respectively. Black circles represent individual predicted values. Numbers (brackets) show the percent change in m ean combined molar AUC24hr at the 5th and 95th percentile relative to the value at the median, based on the linear regression (and 95% CI). The blue line is a linear regression and the gray shaded area the associated 95% CI. The red horizontal line represents combined molar AUC_{24hr} at the median value for the covariate. Plots display the 2.5-97.5 percentile range of the covariate. AUC_{24hr}: area under the plasma concentration-time curve from time 0 to 24 hours; CI: confidence interval; NSCLC: non-small cell lung cancer.

Source: 2.7.2 Clinical Pharmacology Studies; Figure 3.j pg. 113/179

The magnitudes of percent difference in combined molar AUC_{24} at the 5th or 95th percentiles of bilirubin, ALT, or AST relative to the median combined molar AUC_{24} were <15% on both Cycle 1 Day 1 and Cycle 2 Day 1.

In a sensitivity analysis (using the base popPK model as the starting model for covariate evaluation), hepatic function (according to NCI-ODWG criteria) as a categorical covariate was not a statistically significant covariate on the apparent oral clearance of mobocertinib, AP32960, or AP32914, and did not reduce interindividual variability by ≥5%.

According to the applicant, the results indicate that no dose adjustment is necessary for patients with 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).

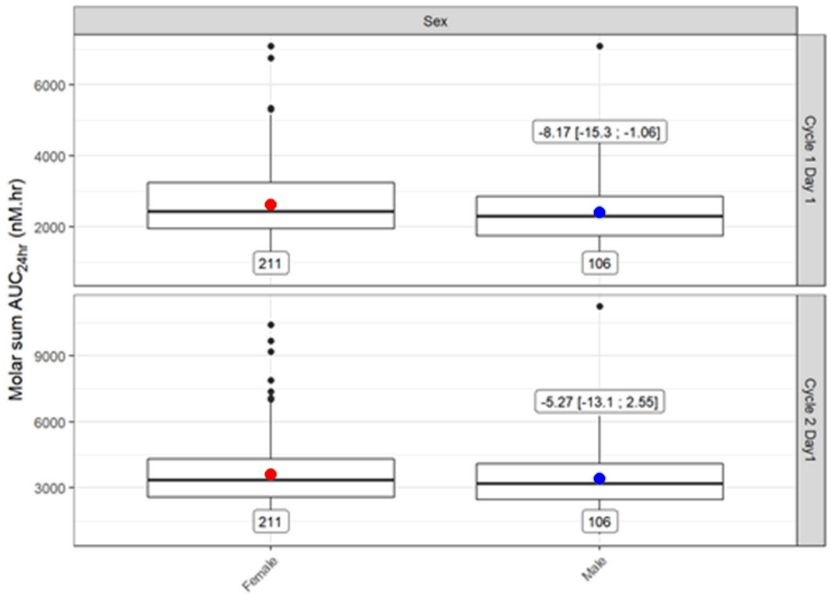
A clinical study is currently ongoing in subjects with moderate or severe hepatic impairment (Study TAK-788-1008) to further evaluate the effect of organ impairment on the PK of mobocertinib and its 2 active metabolites.

- ***Gender***

There was no effect of gender on the PK of mobocertinib and its active metabolites in the population PK analysis.

Individual predicted combined molar exposures of mobocertinib, AP32960, and AP32914 following administration of mobocertinib 160 mg QD to patients with NSCLC were calculated on Cycle 1 Day 1 and Cycle 2 Day 1 using the final model and are presented in the figure below (stratified by sex):

Figure pk 9. Boxplots of Individual Predicted Combined Molar AUC24 of Mobocertinib, AP32960, and AP32914 Stratified by Sex for Patients with NSCLC



Red and blue dots indicate the mean combined molar AUC_{24hr} in the most prevalent category and in other categories, respectively. Numbers (brackets) at the top of the plot represent the percent change in mean combined molar AUC_{24hr} (with 95% CI) in other categories relative to the most prevalent category, while numbers at the bottom of the plot show the number of patients in each category.

AUC_{24hr}: area under the plasma concentration-time curve from time 0 to 24 hours; CI: confidence interval; NSCLC: non-small cell lung cancer.

Source: 2.7.2 Clinical Pharmacology Studies; Figure 3.b pg. 103/179

The magnitudes of percent difference in combined molar AUC_{24} between males and females was <15% on both Cycle 1 Day 1 and Cycle 2 Day 1, suggesting no clinically meaningful difference in exposures between the two groups.

- ***Race***

TAK-788-1003

Study title	A Phase 1/2 Study of the Oral EGFR/HER2 Inhibitor TAK-788 in Japanese Non-Small Cell Lung Cancer Patients
Study design	Phase 1, open-label, multicenter, dose-escalation part of a Phase 1/2 study to evaluate the safety, tolerability and PK of mobocertinib in Japanese patients with locally advanced or metastatic NSCLC. The dose-escalation cohorts started with 40 mg QD and was to be followed by higher dose cohorts until an MTD was determined or 160 mg QD was confirmed to be safe and tolerable in Japanese patients. The size of each cohort was flexible (approximately 3 DLT-evaluable patients for each cohort), and the dose of higher dose cohorts were determined based on an adaptive bayesian logistic regression model (BLRM). The BLRM was established with the broader knowledge of safety, PK and anti-tumor activity of mobocertinib from the Study AP32788-15-101 and also incorporated emerging

	information from previous cohorts. In addition, the sponsor representative and investigators had meeting before opening each cohort to evaluate adequacy of the dose escalation by reviewing safety and available PK or preliminary efficacy data.
Study objectives	*Primary objectives* *To confirm the tolerability of the global maximum tolerated dose (MTD) (160 mg once daily [QD]), identify dose-limiting toxicities (DLTs), and determine recommended phase 2 dose (RP2D) of mobocertinib in Japanese non–small-cell lung cancer (NSCLC) patients.* *Secondary objectives* *- To determine the safety profile of orally administered mobocertinib in Japanese NSCLC patients.* - To determine the pharmacokinetics (PK) of mobocertinib and its active metabolites (including, but not limited to, AP32960 and AP32914) in Japanese NSCLC patients. *- To evaluate the anti-tumor activity of mobocertinib in Japanese NSCLC patients with epidermal growth factor receptor (EGFR) or human epidermal growth factor 2 (HER2) mutations.*
Study period	Date first subject signed informed consent form: 04 February 2019 Date of last subject's last visit/contact: 31 March 2020
No. of subjects	Planned: Approximately 28 to 33 patients Screened: 21 patients Enrolled: 20 patients (16 patients for dose escalation cohorts and 4 patients for 160 mg QD expansion cohort) Analyzed: DLT evaluable population, 16 patients (excluding 4 patients who enrolled in 160 mg QD expansion cohort which was opened after determination of RP2D); Safety population, 20 patients; Pharmacokinetic population, 20 patients; Response-evaluable population, 20 patients.
Treatment	Dose escalation from 40 mg QD to 160 mg QD mobocertinib administered as 40 mg capsules.

Results

Descriptive statistics of plasma PK parameters of mobocertinib on Cycle 1 Day 1 and Cycle 2 Day 1 are provided in the table below:

Table pk 21. Summary of Pharmacokinetic Parameters of Mobocertinib (Pharmacokinetic Population)

			mobocertinib		
			40 mg QD	120 mg QD	160 mg QD
After Single Oral Dose (Cycle 1, Day 1)					
Evaluable Patients, n			4	4	12
t_{max}	h	Median (Min, Max)	3.830 (3.83, 3.88)	3.985 (3.88, 5.92)	3.985 (3.83, 7.87)
C_{max}	ng/mL	Geo Mean (Geo %CV)	15.40 (76.1)	70.28 (56.2)	100.2 (36.3)
AUC_{24}	h*ng/mL	Geo Mean (Geo %CV)	152.9 (62.2)	858.1 (60.3)	1196 (43.0)
Molar C_{av}	nM	Geo Mean (Geo %CV)	10.85 (61.9)	60.82 (59.7)	85.37 (43.3)
Steady State After Multiple Oral Dose (Cycle 2, Day 1)					
Evaluable Patients, n			3	2	5
$t_{max,ss}$	h	Median (Min, Max)	3.950 (3.83, 4.05)	4.000 (3.97, 4.03)	3.970 (3.92, 5.95)
$C_{max,ss}$	ng/mL	Geo Mean (Geo %CV)	17.90 (34.4)	106.2 (39.4)	90.00 (18.4)
$AUC_{24,ss}$	h*ng/mL	Geo Mean (Geo %CV)	214.8 (29.9)	1195 (50.1)	1141 (25.9)
Molar $C_{av,ss}$	nM	Geo Mean (Geo %CV)	15.25 (30.4)	85.14 (51.5)	82.00 (26.1)
$R_{ac(AUC24)}$		Geo Mean (Geo %CV)	1.096 (43.8)	1.260 (12.9)	0.9227 (39.3)
$t_{1/2zeff}$ [a]	h	Geo Mean (Geo %CV)	13.19 (4.3)	10.25 (33.4)	9.137 (19.4)

AUC24: area under the concentration-time curve from time 0 to time 24h; AUC24,ss: area under the concentration-time curve from time 0 to time 24h, at steady state; Cav: average concentration during a dosing interval; Cav,ss: average concentration during a dosing interval, at steady state; Cmax: maximum observed concentration; Cmax,ss: maximum observed concentration during a dosing interval, at steady state; CV: coefficient of variation; Geo Mean: geometric mean; Max: maximum; Min: minimum; QD: once daily; Rac(AUC24): accumulation ratio based on AUC24; t1/2zeff: effective half-life; tmax: time of first occurrence of Cmax; tmax,ss: time of first occurrence of Cmax, at steady state.

Data cut-off 31 March 2020

[a] 40 mg QD: n=2, 120 mg QD: n=2, 160 mg QD: n=3

: PK Parameter after a single or multiple oral doses of 160 mg highlighted by the assessor

Source: Clinical Study Report TAK-788-1003; Table 11.i pg. 71/103

On both Cycle 1 Day 1 and Cycle 2 Day 1, mobocertinib was absorbed into systemic circulation after oral administration, and the C_{max} of mobocertinib was observed approximately 4 hours after the daily dose.

After single-dose administration (Cycle 1 Day 1), C_{max} and AUC_{24} of mobocertinib increased with increased dose-level of mobocertinib: geometric mean of C_{max} (Geo %CV) at 40 mg QD, 120 mg QD, and 160 mg QD were 15.40 ng/mL (76.1), 70.28 ng/mL (56.2), and 100.2 ng/mL (36.3), respectively, and geometric mean of AUC_{24} were 152.9 h*ng/mL (62.2), 858.1 h*ng/mL (60.3), and 1196 h*ng/mL (43.0), respectively.

After repeated doses (Cycle 2 Day 1), $C_{max,ss}$ and $AUC_{24,ss}$ of mobocertinib at 120 mg QD and 160 mg QD were higher compared with 40 mg, however, comparable or slightly decreased with dose-level between 120 mg and 160 mg QD: geometric mean of $C_{max,ss}$ (Geo %CV) at 40 mg QD, 120 mg QD, and 160 mg QD were 17.90 ng/mL (34.4), 106.2 ng/mL (39.4), and dose 90.00 ng/mL (18.4), and geometric mean of $AUC_{24,ss}$ (Geo %CV) were 214.8 h*ng/mL (29.9), 1195 h*ng/mL (50.1), and 1141 h*ng/mL (25.9), respectively.

Pooled analyses from the individual PK exposure data at 40 mg, 120 mg, and 160 mg QD, showed that $C_{max,ss}$ and $AUC_{24,ss}$ of mobocertinib increased in an approximately dose-proportional manner over the dose range of 40 to 160 mg QD, assessed by a power model with the coefficient (90% CI) of 1.215 (0.892, 1.539) for $C_{max,ss}$ and 1.244 (0.920, 1.568) for $AUC_{24,ss}$, respectively, as the slopes of power models for both $C_{max,ss}$ and $AUC_{24,ss}$ were approximately equal to 1.0 and the value of 1.0 was contained

within the 90% CIs of slopes. Regarding to Cycle 1 Day 1 C_{max} and AUC_{24}, 1 was not contained within 90% CIs for the slopes of power models.

Systemic exposure (AUC_{24}) was slightly accumulated at 40 mg QD and moderately accumulated at 120 mg QD, but decreased at 160 mg QD ($R_{ac(AUC24)}$: 1.096, 1.260, and 0.9227, respectively). The decrease at 160 mg QD suggests autoinduction of the apparent oral clearance of mobocertinib likely via induction of CYP3A at 160 mg dose.

The terminal elimination half-life time of mobocertinib could not be characterized due to the daily dose regimen and the short washout period. The geometric mean of effective half-life based on accumulation was in the range of 9 to 13 hours across 40 to 160 mg mobocertinib QD.

Active Metabolites AP32960 and AP32914

PK parameter for the active metabolites after single and multiple doses are given in the tables below:

Table pk 22. Summary of Pharmacokinetic Parameters of AP32960 (Pharmacokinetic Population)

			mobocertinib		
			40 mg QD	120 mg QD	160 mg QD
After Single Oral Dose (Cycle 1, Day 1)					
Evaluable Patients, n			4	4	12
t_{max}	h	Median (Min, Max)	3.830 (3.83, 5.88)	3.985 (3.88, 5.92)	4.965 (3.83, 7.87)
C_{max}	ng/mL	Geo Mean (Geo %CV)	8.797 (96.4)	28.81 (31.0)	47.84 (28.9)
AUC_{24}	h*ng/mL	Geo Mean (Geo %CV)	86.06 (77.2)	378.2 (35.3)	569.9 (27.1)
Molar C_{av}	nM	Geo Mean (Geo %CV)	6.269 (77.3)	27.51 (35.0)	41.70 (27.4)
Molar AUC_{24} Ratio [a]		Geo Mean (Geo %CV)	0.5774 (33.6)	0.4525 (29.8)	0.4888 (32.1)
Steady State After Multiple Oral Dose (Cycle 2, Day 1)					
Evaluable Patients, n			3	2	5
$t_{max,ss}$	h	Median (Min, Max)	3.950 (3.83, 4.05)	4.000 (3.97, 4.03)	3.970 (3.92, 5.95)
$C_{max,ss}$	ng/mL	Geo Mean (Geo %CV)	12.34 (68.7)	59.94 (24.3)	56.85 (21.0)
$AUC_{24,ss}$	h*ng/mL	Geo Mean (Geo %CV)	158.6 (63.1)	794.0 (36.6)	750.3 (27.4)
Molar $C_{av,ss}$	nM	Geo Mean (Geo %CV)	11.57 (63.7)	58.16 (38.2)	55.27 (27.8)
$R_{ac(AUC24)}$		Geo Mean (Geo %CV)	1.393 (17.5)	1.765 (2.0)	1.366 (15.9)
$t_{1/2eff}$	h	Geo Mean (Geo %CV)	12.63 (39.2)	19.79 (4.3)	12.11 (30.6)
Molar $AUC_{24,ss}$ Ratio [b]		Geo Mean (Geo %CV)	0.7583 (30.8)	0.6817 (11.6)	0.6740 (9.8)

AUC24: area under the concentration-time curve from time 0 to time 24h; AUC24,ss: area under the concentration-time curve from time 0 to time 24h, at steady state; Cav: average concentration during a dosing interval; Cav,ss: average concentration during a dosing interval, at steady state; Cmax: maximum observed concentration; Cmax,ss: maximum observed concentration during a dosing interval, at steady state; CV: coefficient of variation; Geo Mean: geometric mean; Max: maximum; Min: minimum; QD: once daily; Rac(AUC24): accumulation ratio based on AUC24; t1/2zeff: effective half-life; tmax: time of first occurrence of Cmax; tmax,ss: time of first occurrence of Cmax, at steady state.

Data cut-off 31 March 2020

Source: Clinical Study Report TAK-788-1003; Table 11.j pg. 75/103

Table pk 23. Summary of Pharmacokinetic Parameters of AP32914 (Pharmacokinetic Population)

			mobocertinib		
			40 mg QD	120 mg QD	160 mg QD
After Single Oral Dose (Cycle 1, Day 1)					
Evaluable Patients, n			4	4	12
t_{max}	h	Median (Min, Max)	3.830 (3.83, 5.88)	4.995 (3.88, 5.98)	4.965 (3.83, 7.87)
C_{max}	ng/mL	Geo Mean (Geo %CV)	1.677 (66.2)	4.962 (41.7)	8.626 (40.6)
AUC_{24} [a]	h*ng/mL	Geo Mean (Geo %CV)	20.15 (39.6)	70.58 (45.6)	105.9 (44.5)
Molar C_{av} [a]	nM	Geo Mean (Geo %CV)	1.466 (39.2)	5.133 (45.3)	7.758 (45.0)
Molar AUC_{24} Ratio [a, c]		Geo Mean (Geo %CV)	0.1054 (6.8)	0.08437 (43.3)	0.09084 (18.7)
Steady State After Multiple Oral Dose (Cycle 2, Day 1)					
Evaluable Patients, n			3	2	5
$t_{max,ss}$	h	Median (Min, Max)	3.950 (3.83, 4.05)	4.000 (3.97, 4.03)	3.980 (3.92, 5.95)
$C_{max,ss}$	ng/mL	Geo Mean (Geo %CV)	1.808 (31.4)	9.198 (37.7)	7.920 (13.3)
$AUC_{24,ss}$	h*ng/mL	Geo Mean (Geo %CV)	21.02 (24.3)	116.9 (49.7)	105.0 (20.4)
Molar $C_{av,ss}$	nM	Geo Mean (Geo %CV)	1.531 (25.0)	8.535 (51.1)	7.720 (20.4)
$R_{ac\ (AUC24)}$		Geo Mean (Geo %CV)	1.044 (41.7)	1.414 (21.2)	1.027 (34.5)
$t_{1/2zeff}$ [b]	h	Geo Mean (Geo %CV)	11.53 (9.2)	12.99 (46.9)	10.59 (29.0)
Molar $AUC_{24,ss}$ Ratio [d]		Geo Mean (Geo %CV)	0.1003 (8.9)	0.1005 (0.7)	0.09389 (9.4)

AUC24: area under the concentration-time curve from time 0 to time 24h; AUC24,ss: area under the concentration-time curve from time 0 to time 24h, at steady state; Cav: average concentration during a dosing interval; Cav,ss: average concentration during a dosing interval, at steady state; Cmax: maximum observed concentration; Cmax,ss: maximum observed concentration during a dosing interval, at steady state; CV: coefficient of variation; Geo Mean: geometric mean; Max: maximum; Min: minimum; QD: once daily; Rac(AUC24): accumulation ratio based on AUC24; t1/2zeff: effective half-life; tmax: time of first occurrence of Cmax; tmax,ss: time of first occurrence of Cmax, at steady state.

Data cut-off 31 March 2020

[a] 40 mg QD: n=3, 120 mg QD: n=4, 160 mg QD: n=12

[b] 40 mg QD: n=2, 120 mg QD: n=2, 160 mg QD: n=3

[c] (Molar AUC_{24} of AP32914)/(Molar AUC_{24} of mobocertinib)

[d] (Molar $AUC_{24,ss}$ of AP32914)/(Molar $AUC_{24,ss}$ of mobocertinib)

Source: Clinical Study Report TAK-788-1003; Table 11.k pg. 79/103

Comparison of exposure in Asians vs non-Asians.

The effect of race on the PK of mobocertinib and its active metabolites was investigated in the popPK analysis and was not determined to be a statistically significant covariate. The applicant has also compared PK parameters (derived using noncompartmental analysis of intensive PK data) for Asian and non-Asian patients who received 160 mg QD mobocertinib and were enrolled in Parts 1 and 2 of Study 101, or the phase 1 part of Study TAK-788-1003 (Study 1003). After both single- and multiple-dose administration, geometric mean Cmax and AUC24 values for mobocertinib, AP32960, AP32914, and combined molar sum were similar between Asian and non-Asian patients, with substantial overlap observed in the distribution of Cmax and AUC24 values in the two patient populations. Sparse PK data were also compared between Asian and non-Asian patients who received 160 mg QD mobocertinib in Studies 101 and 1003 and who were included the popPK analysis dataset. Median predose

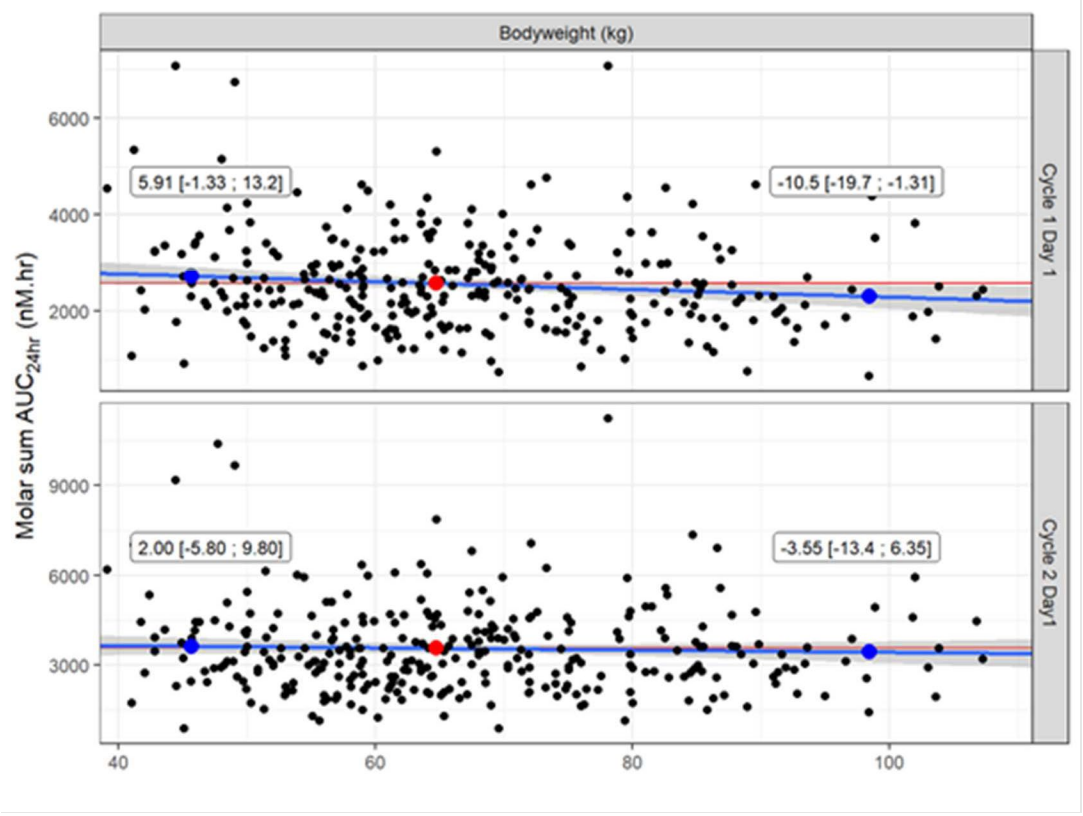
concentrations of mobocertinib, AP32960, AP32914 and combined molar sum were generally similar for the two groups on Day 1 of Cycles 2, 3, 4, and 5, and considerable overlap was observed in the distributions of predose concentrations.

- ***Weight***

Body weight was not identified as a statistically significant covariate in the population PK analysis. This would indicate that the PK of mobocertinib and its active metabolites is similar across the body weight range (37.3 kg to 132 kg) examined.

Individual predicted combined molar exposures of mobocertinib, AP32960, and AP32914 following administration of mobocertinib 160 mg QD to patients with NSCLC were calculated on Cycle 1 Day 1 and Cycle 2 Day 1 using the final model and are presented versus body weight in the figure below:

Figure pk 10. Individual Predicted Combined Molar AUC24 of Mobocertinib, AP32960, and AP32914 Versus Body Weight for Patients with NSCLC



Red and blue circles indicate the median and 5th and 95th percentiles of individual covariate values, respectively. Black circles represent individual predicted values. Numbers (brackets) show the percent change in m ean combined molar AUC24hr at the 5th and 95th percentile relative to the value at the median, based on the linear regression (and 95% CI). The blue line is a linear regression and the gray shaded area the associated 95% CI. The red horizontal line represents combined molar AUC_{24hr} at the median value for the covariate. Plots display the 2.5-97.5 percentile range of the covariate.
AUC_{24hr}: area under the plasma concentration-time curve from time 0 to 24 hours; CI: confidence interval; NSCLC: non-small cell lung cancer.

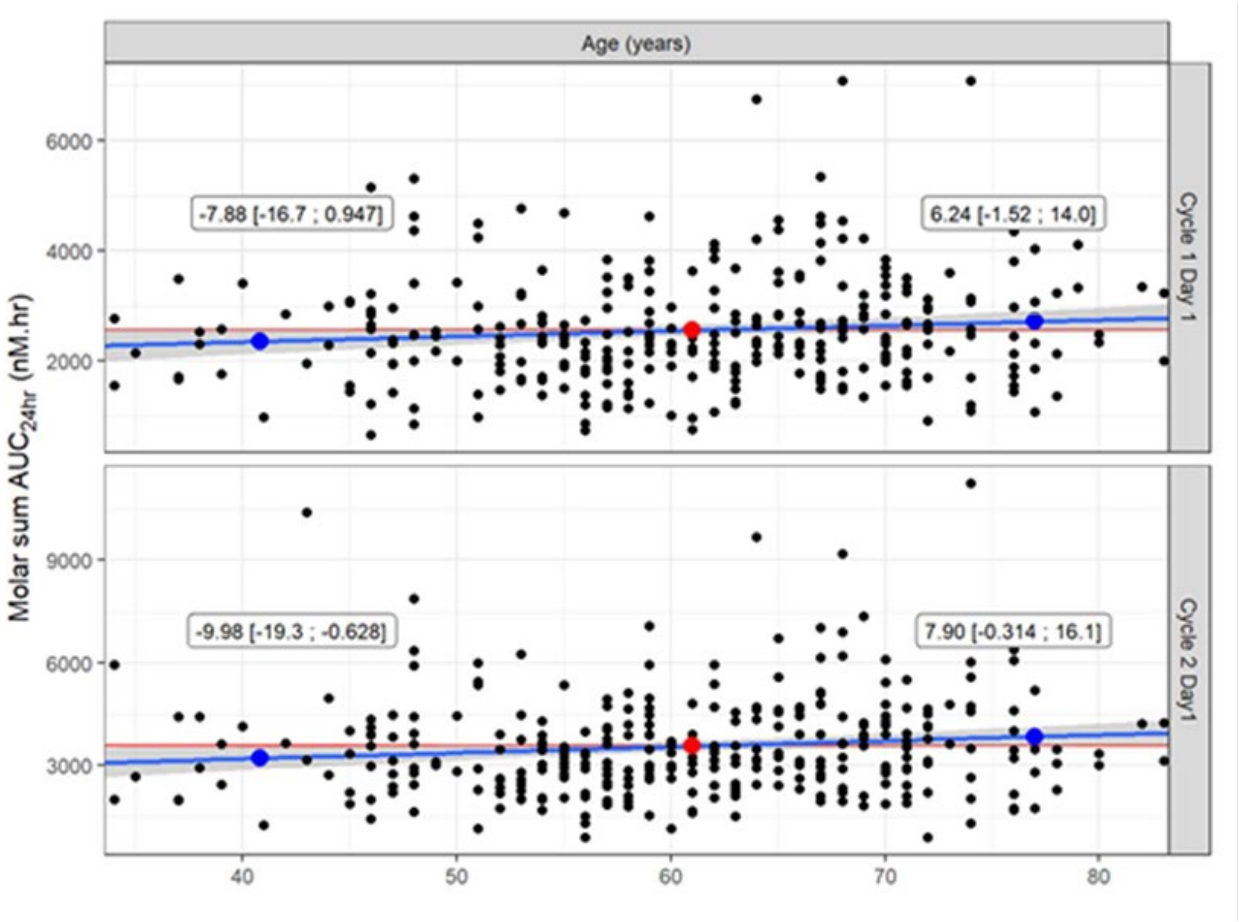
Source: 2.7.2 Clinical Pharmacology Studies; Figure 3.c pg. 105/179

The magnitudes of percent difference in combined molar AUC_{24} at the 5th or 95th percentiles of body weight relative to the median combined molar AUC_{24} were <15% on both Cycle 1 Day 1 and Cycle 2 Day 1. These observed differences are well below the variability in combined molar AUC24 observed across the entire analysis population, where the 5th and 95th percentiles were -46.8% to +191% relative to the median combined molar AUC_{24}.

- ***Elderly***

In the population PK analysis, age was not identified as a statistically significant covariate, indicating that the PK of mobocertinib and its active metabolites is similar across the age range (18 to 86 years) examined. In addition, individual predicted combined molar exposures of mobocertinib, AP32960, and AP32914 following administration of mobocertinib 160 mg QD to patients with NSCLC were calculated on Cycle 1 Day 1 and Cycle 2 Day 1 using the final model and are presented versus age in the figure below:

Figure pk 11. Individual Predicted Combined Molar AUC24 of Mobocertinib, AP32960, and AP32914 Versus Age for Patients with NSCLC



Red and blue circles indicate the median and 5th and 95th percentiles of individual covariate values, respectively. Black circles represent individual predicted values. Numbers (brackets) show the percent change in m ean combined molar AUC24hr at the 5th and 95th percentile relative to the value at the median, based on the linear regression (and 95% CI). The blue line is a linear regression and the gray shaded area the associated 95% CI. The red horizontal line represents combined molar AUC24hr at the median value for the covariate. Plots display the 2.5-97.5 percentile range of the covariate.

AUC24hr: area under the plasma concentration-time curve from time 0 to 24 hours; CI: confidence interval; NSCLC: non-small cell lung cancer.

Source: 2.7.2 Clinical Pharmacology Studies; Figure 3.a pg. 102/179

The magnitudes of percent difference in combined molar AUC_{24} at the 5th or 95th percentiles of age relative to the median combined molar AUC_{24} were <15% on both Cycle 1 Day 1 and Cycle 2 Day 1. These observed differences are well below the variability in combined molar AUC_{24} observed across the entire analysis population, where the 5th and 95th percentiles were -46.8% to +191% relative to the median combined molar AUC_{24}.

- ***Children***

The PK of mobocertinib has not been characterized in paediatric patient populations.

Pharmacokinetic interaction studies

In vitro and clinical studies, as well as PBPK analyses, have been conducted to investigate the potential for DDIs between mobocertinib and coadministered drugs:

- ***In vitro***

CYP enzymes

Victim

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

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.

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.

Perpetrator

As outlined in the submitted Clinical Overview, *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. This was stated to be the rationale that 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

Victim

With regard to transporter-based interactions, it was stated that 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 (Module 2.7.2 Section 3.1.6).

Perpetrator

It was stated that 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. The applicant

therefore concluded that mobocertinib is not expected to result in clinically meaningful inhibition of P-gp or BCRP *in vivo*.

Mobocertinib was not found to be 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*. A PBPK model predicted no clinically meaningful effect of multiple-dose administration of 160 mg QD mobocertinib on the PK of metformin, a probe substrate for OCT1 and MATE. The applicant therefore concluded that the potential for *in vivo* inhibition of these transporters was inferred to be low.

In vivo

The effect of extrinsic factors on mobocertinib PK are investigated in *in vivo* in studies listed below:

Table pk 24. Clinical Studies investigating the effect of extrinsic factors on mobocertinb PK

Study Identifier and Status	Objective(s) of the Study	Study Design and Type of Control	Dosage Regimen[a]	Participants
TAK-788-1006 Completed	DDI with **strong CYP3A inhibitor** (itraconazole) or **strong CYP3A inducer** (rifampin)	Phase 1, open-label, 2-part (part 1 inhibitor/ part 2 inducer), PK study	**Part 1** Single dose of mobocertinib 20 mg on Period 1 Day 1 and Period 2 Day 5 Oral itraconazole 200 mg QD on Period 2 Days 1 to 14 **Part 2** Single dose of mobocertinib 160 mg on Period 1 Day 1 and Period 2 Day 7 Oral rifampin 600 mg QD on Period 2 Days 1 to 13	Healthy adult subjects (N=24)
TAK-788-1004 Completed	DDI with midazolam	Phase 1, 2-part, open-label, PK study	Part A (Cycle 1, PK cycle): Oral midazolam 3 mg on Days 1 and 24 IV midazolam 1 mg on Days 2 and 25 Mobocertinib 160 mg QD on Days 3 to 30 Part B (Cycle 2 to 24): Mobocertinib 160 mg QD	Patients with locally advanced or metastatic NSCLC (N=13 PK dataset) (N=26 safety dataset)

a Route of administration used in studies was oral

- **Mobocertinib Effect on Other Drugs**

CYP inhibition/induction

In study TAK-788-1004, the effect of mobocertinib on oral and IV midazolam PK has been assessed in a fixed- sequence DDI study design:

TAK-788-1004

Study title A Phase 1, 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

Study design	This phase 1, open-label, multicenter, drug-drug interaction study consisted of 2 parts: Part A (Cycle 1: PK cycle) and Part B (Cycle 2 to Cycle 24: Treatment Cycles). The patient population consisted of adult patients with locally advanced or metastatic NSCLC that was refractory to standard available therapies. In Part A of the study, a fixedsequence design over a single 30-day duration including 28 days of treatment with mobocertinib was used (Cycle 1: PK Cycle and Cycle 2 Day 1). After screening, eligible patients were enrolled and received a single oral dose of midazolam 3 mg on Days 1 and 24 and a single IV dose of midazolam 1 mg as a 5-minute infusion on Days 2 and 25. Patients also received mobocertinib 160 mg QD orally on Days 3 through Day 30. Serial PK blood samples were collected to measure plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam in the absence and presence of mobocertinib. In addition, mobocertinib PK blood samples were collected prior to dosing on Cycle 1 Days 24, 25, 26 and Cycle 2 Day 1 and after dosing on Day 24 to assess plasma concentrations of mobocertinib and its active metabolites AP32960 and AP32914. Further, biomarker blood samples were collected on Days 1 and 24 prior to dosing, to measure plasma concentrations of 4β-hydroxycholesterol and cholesterol. In addition, circulating tumor DNA samples were collected as part of assessments during Cycles 1, 3, and 5, and at the time of progressive disease (PD).
Study objectives	*Primary objectives* The primary objective of this study was to characterize the effect of repeated oral administration of mobocertinib 160 mg once daily (QD) on the single oral- and intravenous (IV)-dose pharmacokinetics (PK) of midazolam. *Secondary Objective:* The secondary objective of this study is to assess the safety and tolerability of mobocertinib in patients with advanced non–small cell lung cancer (NSCLC). *Exploratory Objective:* The exploratory objectives of this study are as follows: - To assess the oral bioavailability of midazolam (both IV and oral) in the presence and absence of mobocertinib. - To assess steady state of mobocertinib achieved in Cycle 1. - To assess the potential cytochrome P450 (CYP)3A induction of mobocertinib using an endogenous CYP3A biomarker.
Study period	Date first subject signed informed consent form: 23 December 2019 Date of last subject's last visit/contact: 17 December 2020 (*Note: Study is still ongoing, dates reflect time points as relevant to the primary endpoint*)
No. of subjects	Planned: 26 subjects Enrolled: 26 subjects (Part A) Analyzed: 24 subjects Completed Part A: 13 patients Ongoing: 10 patients
Treatment	*Part 1 (30 days):* Midazolam was administered at clinic on study Days 1, 2, 24, and Day 25. Mobocertinib was self-administered orally at home at 160 mg QD, on Days 3

through 30, except on Days 3, 24, 25, and 26, on which the mobocertinib 160 mg dose was administered in the clinic.

Part B (*28-Day* Cycles): Patients continued into Part B at the mobocertinib dose that they were receiving (and tolerating) at the end of Part A and continued treatment until Cycle 24, or until the first incidence of PD, unacceptable toxicity, or another discontinuation criterion is met.

Results

Adult patients with locally advanced or metastatic non-small-cell lung cancer who were refractory or who had relapsed to standard therapies were administered a single oral dose of midazolam 3 mg on Cycle 1 Day 1, followed by a single dose of IV midazolam 1 mg on Cycle 1 Day 2, both without mobocertinib coadministration. After PK sampling for midazolam PK characterization over 24 hours, mobocertinib 160 mg QD was administered orally from Day 3 onward to achieve a steady-state concentration. After achievement of steady-state for mobocertinib, midazolam was administered as a single oral 3 mg dose on Cycle 1 Day 24, followed by a single IV 1 mg dose on Cycle 1 Day 25.

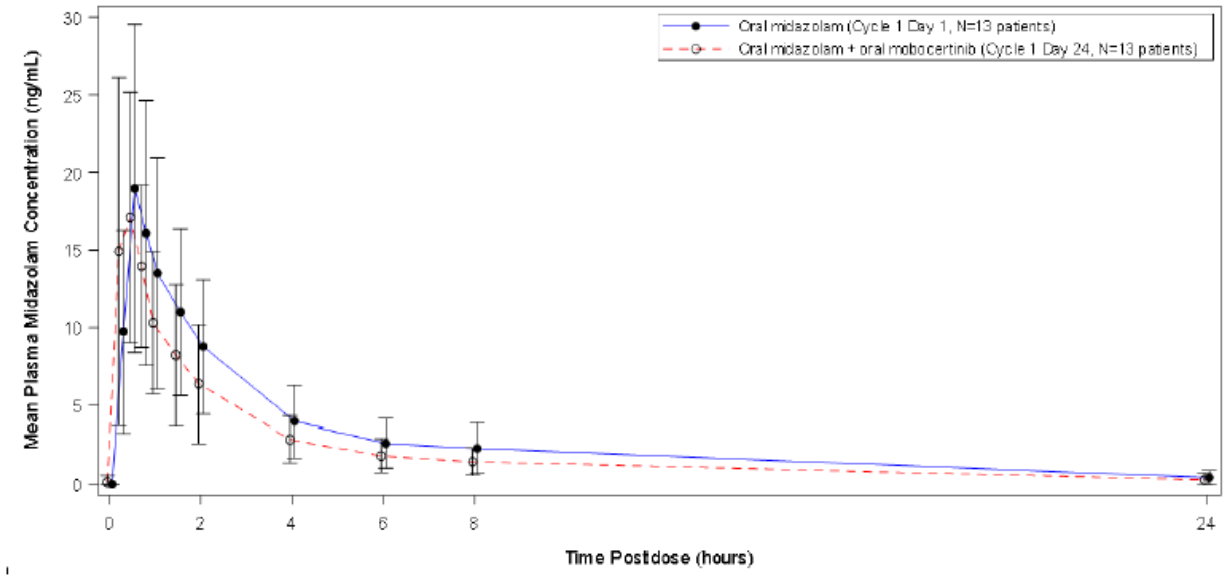
The noncompartmental PK parameters of midazolam and its metabolite 1-hydroxymidazolam, along with mobocertinib and its active metabolites, AP32914 and AP32960, were derived from the concentration-time data for all patients who received at least 1 dose of mobocertinib (i.e., Safety Analysis Set). However, only PK parameters from the PK-evaluable population were included in the summary statistics and ANOVA analyses.

A total of 26 patients with locally advanced or metastatic non-small-cell lung cancer who were refractory or who had relapsed to standard therapies were enrolled in this study, and subsequently were included in the safety analysis population. As per the protocol and Clinical Pharmacology Analysis Plan, 13 of 26 patients were considered PK-evaluable as they met the criteria. The other 13 patients were not considered PK evaluable for the following reasons: 9 patients experienced a dose interruption within 1 week before Cycle 1 Day 24; 3 patients experienced dose reduction before Cycle 1 Day 26; and 1 patient experienced intermittent vomiting coinciding with Cycle 1 Day 24 dosing and whose mobocertinib AUC_{∞} was lower than the 10th percentile of mobocertinib AUC_{∞} among the 13 PK-evaluable patients.

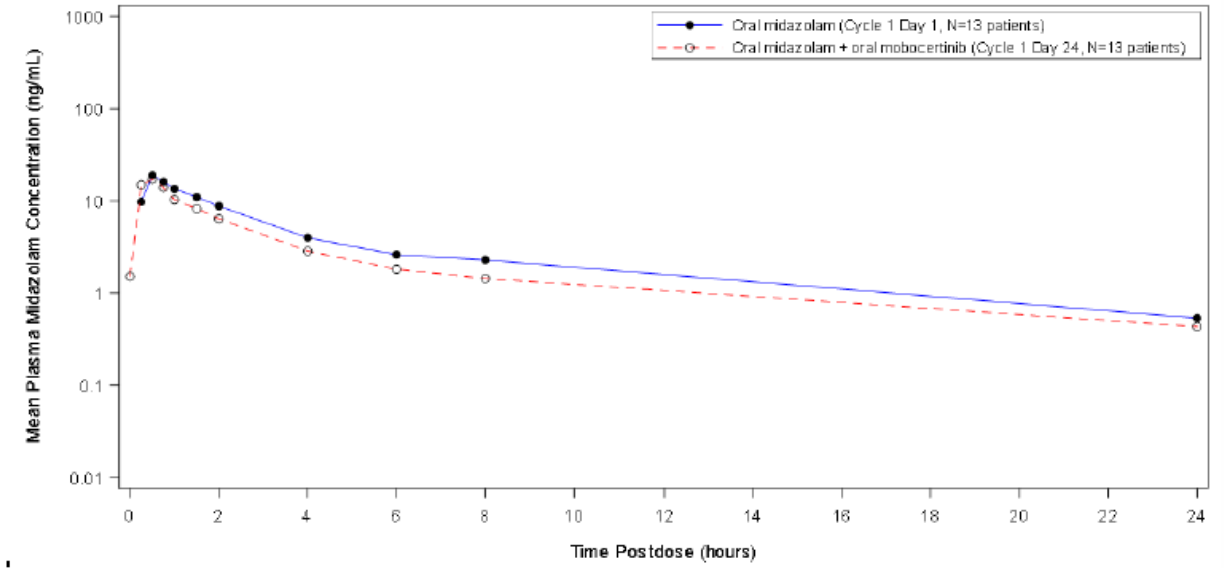
Results are presented below:

Figure pk 12. Arithmetic Mean (SD) Plasma Midazolam Concentration-Time Profiles Following Administration of a Single Oral Dose of 3 mg Midazolam Alone (Cycle 1 Day 1) and in the Presence of 160 mg QD Mobocertinib (Cycle 1 Day 24), PK-Evaluable Population

Linear Scale



Semi-Log Scale

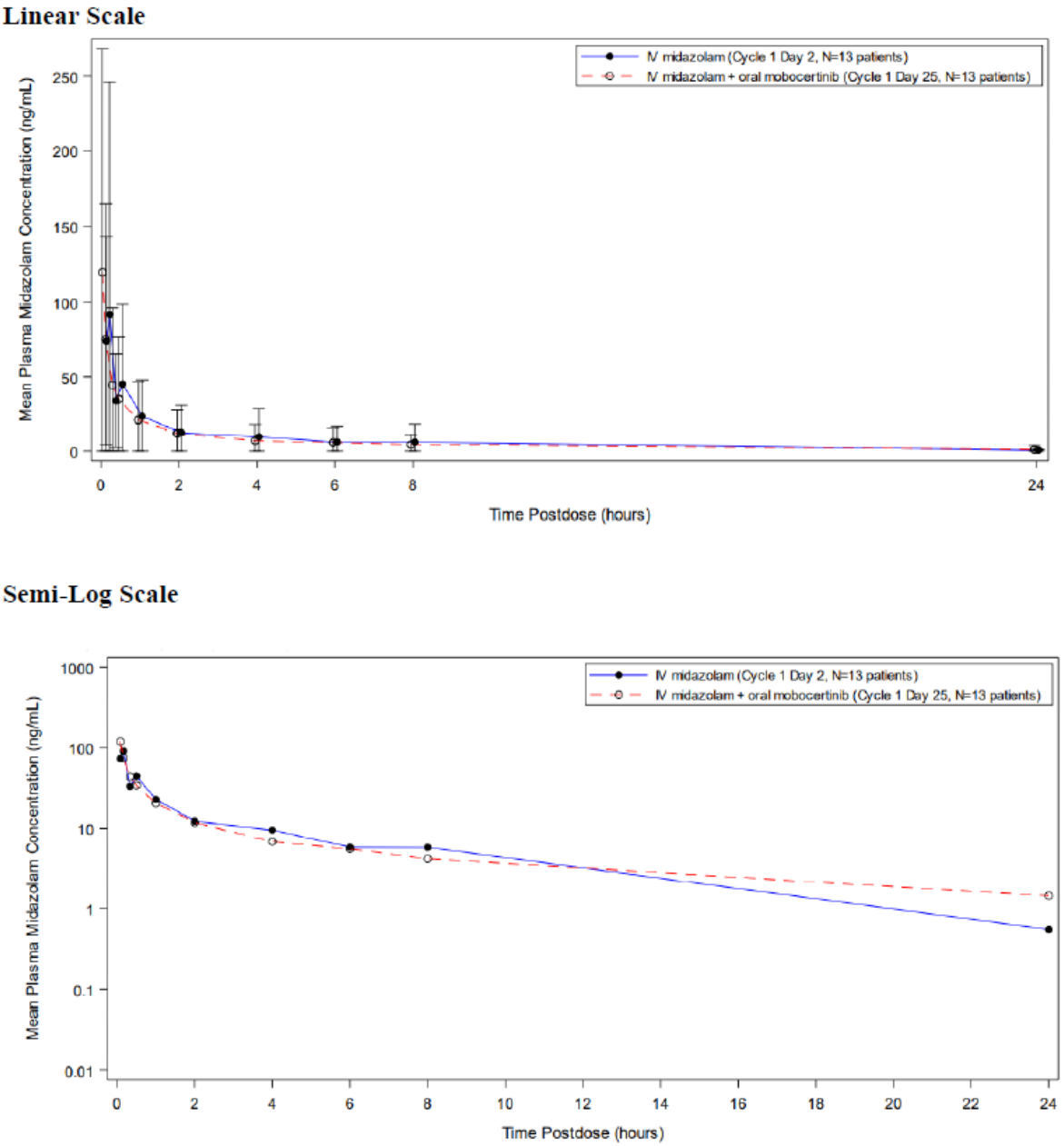


QD: once daily; IV: intravenous.

PK profiles have been shifted to distinguish mean and error bars between treatments.

Source: Clinical Study Report TAK-788-1004; Figure 11a pg. 74/124

Figure pk 13. Arithmetic Mean (SD) Plasma Midazolam Concentration-Time Profiles Following Administration of a Single IV Dose of 1 mg Midazolam Alone (Cycle 1 Day 2) and in the Presence of 160 mg QD Mobocertinib (Cycle 1 Day 25), PK-Evaluable Population



QD: once daily; IV: intravenous.

Source: Clinical Study Report TAK-788-1004; Figure 11b pg. 75/124

Table pk 25. Plasma PK Parameters and Geometric LS Mean Ratios of Oral (3 mg) and IV (1 mg) Midazolam With vs Without 160 mg QD Mobocertinib Coadministration in Cancer Patients, PK-Evaluable Population

Parameter (unit)	Midazolam Alone [a] (Reference)	Midazolam and Mobocertinib [a] (Test)	Geometric LS Mean Ratio (90% CI) (Test/Reference) [b]
Oral Midazolam			
N	13	13	
t_{max} (h)	0.517 (0.467 to 2.00)	0.533 (0.250 to 1.00)	
C_{max} (ng/mL)	17.0 (60.2)	17.5 (60.7)	1.03 (0.739, 1.42)
AUC_{last} (ng*h/mL)	53.5 (61.1)	39.6 (65.9)	0.740 (0.580, 0.943)
AUC_{∞} (ng*h/mL)	58.3 (61.0)	39.0 (61.4) [c]	0.676 (0.532, 0.859)
$t_{1/2z}$ (h)	5.33 (51.7)	3.56 (61.6) [c]	
IV Midazolam			
N	13	13	
t_{max} (h)	0.0500 (0.00-1.00)	0.0500 (0.00-0.500)	
C_{max} (ng/mL)	70.8 (151)	92.2 (132)	1.30 (0.886, 1.92)
AUC_{last} (ng*h/mL)	85.3 (116)	79.0 (123)	0.926 (0.723, 1.19)
AUC_{∞} (ng*h/mL)	90.4 (113)	71.6 (96.0) [c]	0.837 (0.673, 1.04)
$t_{1/2z}$ (h)	5.47 (50.9)	3.97 (58.9) [c]	
Oral Bioavailability			
F (%)	21.5 (107)	21.7 (80.0) [d]	

%CV: percent coefficient of variation; AUC∞: area under the concentration-time curve, from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; AUClast: area under the concentration-time curve from time 0 to time of the last quantifiable concentration; Cmax: maximum observed plasma concentration; F:
absolute bioavailability; IV: intravenous; PK: pharmacokinetic; t1/2z: terminal disposition phase half-life; QD: once daily; tmax: time of first occurrence of Cmax.
A linear mixed effect model on the natural log-transformed parameters was performed with treatment as a fixed effect and subject as a random effect. The LS means and difference of LS means for the log-transformed parameters were exponentiated to obtain the point estimates and 90% CIs of the geometric LS mean ratio on the original scale.
The statistical analysis was performed on Cmax, AUClast, and AUC∞ parameters only.
Midazolam alone: 3 mg oral midazolam administered following fasting for at least 2 hours on Cycle 1 Day 1 or 1 mg IV midazolam with or without food on Cycle 1 Day 2.
Midazolam and mobocertinib: 3 mg oral midazolam administered following fasting for at least 2 hours on Cycle 1 Day 24 or 1 mg IV midazolam and 160 mg QD mobocertinib with or without a low-fat meal on Cycle 1 Day 25.
a Parameters are presented as geometric mean (geometric %CV) except for tmax, which is presented as median (range).
b The geometric LS mean ratio is calculated for Cmax, AUClast, and AUC∞ parameters only.
c N = 12.
d N = 11.

Source: Clinical Study Report TAK-788-1004; Table 11.j pg. 77/124

As outlined in the table and illustrated in the figures above:

Statistical analysis comparing systemic exposures of midazolam after a single oral dose of midazolam coadministered with mobocertinib to oral midazolam alone resulted in geometric LS mean ratios (90% CI) for Cmax, AUClast and AUC∞ of 1.03 (0.739, 1.42), 0.740 (0.580, 0.943) and 0.676 (0.532, 0.859), respectively.

Similarly, statistical analysis comparing systemic exposures of midazolam after a single IV dose of midazolam coadministered with mobocertinib versus IV midazolam alone resulted in geometric LS mean ratios (90% CI) for Cmax, AUClast and AUC∞ of 1.30 (0.886, 1.92), 0.926 (0.723, 1.19) and 0.837 (0.673, 1.04), respectively.

Thus, mobocertinib increased oral midazolam Cmax by approximately 3% but decreased midazolam AUClast and AUC∞ by approximately 26% and 32%, respectively.

Additionally, mobocertinib increased IV midazolam Cmax by approximately 30% but decreased the AUClast and AUC∞ by approximately 7% and 16%, respectively.

Available non-clinical data and simulations indicate that mobocertinib may reduce plasma concentrations of coadministered medications that are predominantly metabolised by CYP3A. The concomitant use of mobocertinib with CYP3A substrates can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates.

Based on the results of *in vitro* studies, mobocertinib may also induce other enzymes and transporters (e.g., CYP2C, P-glycoprotein [P-gp]) via the same mechanism responsible for induction of CYP3A (e.g., pregnane X receptor activation).

Transporter

The potential of mobocertinib to interact with transporters has not been investigated in clinical studies.

- **Effect of Other Drugs on mobocertinib**

CYP3A4 Inhibitors

In vitro studies suggested that mobocertinib is mainly metabolized by CYP3A4 (see above). As co-administration with inhibitors or inducers of CYP3A4 has the potential to affect mobocertinib exposure, a clinical DDI study was conducted to assess the effect of a strong CYP3A4 inhibitor (itraconazole) and a strong CYP3A4 inducer (Rifampin) on the PK of mobocertinib:

TAK-788-1006

Study title	A Phase 1 Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects
Study design	This was a 2-part study. Each part was conducted as an open-label, 2-period, fixed-sequence study with TAK-788 designed to characterize TAK-788 drug-drug interaction (DDI) with either a strong CYP3A inhibitor, itraconazole (Part 1), or with a strong CYP3A inducer, rifampin (Part 2), in healthy adult subjects. Subjects participating in Part 1 were different from those participating in Part 2.
Study objectives	*Primary objectives* *Part 1:* To characterize the effect of itraconazole, a strong Cytochrome P450 (CYP) 3A inhibitor, on the single-dose pharmacokinetic (PK) of TAK-788 and its active metabolites (AP32960 and AP32914) in healthy adult subjects. *Part 2:* To characterize the effect of rifampin, a strong CYP3A inducer, on the single-dose PK of TAK-788 and its active metabolites (AP32960 and AP32914) in healthy adult subjects. *Exploratory Objective:* *Part 1 and Part 2:* To assess the safety data of TAK-788 following single oral dose with/without strong CYP3A Inhibitor or inducer in healthy adult subjects.
Study period	Date first subject signed informed consent form: 02 May 2019 Date of last subject's visit/contact: 16 August 2019.
No. of subjects	Planned: up to 28 subjects Enrolled: 24 subjects Analyzed: 24 subjects

(A total of 12 subjects entered and completed Part 1 of the study and 12 subjects entered and completed Part 2 of the study.)

Treatment

Part 1: TAK-788 assessment with itraconazole

On Day 1 of Period 1, subjects received a single oral dose of 20 mg TAK-788. On Day 1 to Day 14 of Period 2, subjects received 200 mg itraconazole QD, coadministered on Day 5 with a single oral dose of 20 mg TAK-788.

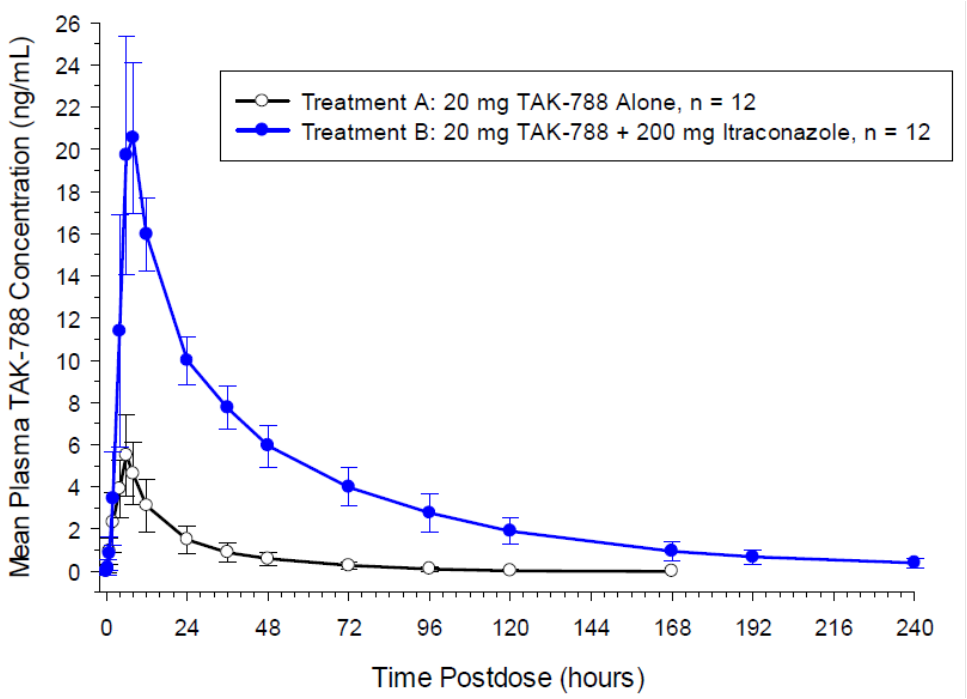
Part 2: TAK-788 assessment with rifampin

On Day 1 of Period 1, subjects received a single oral dose of 160 mg TAK-788. On Day 1 to Day 13 of Period 2, subjects received 600 mg rifampin QD, coadministered on Day 7 with a single oral dose of 160 mg TAK-788.

Results

The study results indicate a significant drug interaction between mobocertinib and itraconazole after co-administration of multiple doses of itraconazole:

Figure pk 14. Arithmetic Mean (SD) Plasma TAK-788 Concentration-Time Profiles Following Administration of a Single Oral Dose of 20 mg TAK-788 Alone (Treatment A) and Coadministration of Multiple Oral Doses of 200 mg Itraconazole QD with a Single Oral Dose of 20 mg TAK-788 (Treatment B) in Healthy Subjects (Linear Scale) (PK Set) (Part 1)



Source: Clinical Study Report TAK-788-106; Figure 11a pg. 59/99

The plasma TAK-788 profiles were generally well characterized in Part 1 following both treatments. Plasma TAK-788 concentrations were detectable in all subjects by 1 hour and remained quantifiable in all subjects through 72 and 240 hours following administration of 20 mg TAK-788 alone and 200 mg itraconazole + 20 mg TAK-788, respectively. Peak mean plasma TAK-788 concentrations were reached at approximately 6 and 8 hours following 20 mg TAK-788 alone and 200 mg itraconazole + 20 mg TAK-788, respectively. The mean concentrations of TAK-788 were higher throughout the entire sampling interval when TAK-788 was administered with itraconazole compared to when TAK-788 was administered alone.

Table pk 6. Plasma Pharmacokinetic Parameters of TAK-788 and Its 2 Active Metabolites AP32960 and AP32914 Following Coadministration of Multiple Oral Doses of 200 mg Itraconazole QD with a Single Oral Dose of 20 mg TAK-788 (Treatment B) Versus Administration of a Single Oral Dose of 20 mg TAK-788 Alone (Treatment A) in Healthy Subjects (Part 1)

Parameter (unit)	TAK-788 alone[a] (Reference)	TAK-788 + Itraconazole[a] (Test)	Geometric LS Mean Ratio (90% CI) (Test/Reference)[b]
TAK-788			
t_{max} (hr)	6.00 (2.00-8.00) [n=12]	8.00 (5.99-12.00) [n=12]	-
C_{max} (ng/mL)	5.52 (34.1) [n=12]	21.1 (19.0) [n=12]	3.83 (3.25-4.50)
AUC_{∞} (ng·hr/mL)	106 (40.0) [n=12]	892 (20.0) [n=12]	8.43 (7.02-10.12)
$t_{1/2z}$ (hr)	21.2 (16.7) [n=12]	53.9 (18.2) [n=12]	-
AP32960			
t_{max} (hr)	6.00 (2.00-6.01) [n=12]	8.00 (6.00-12.00) [n=12]	-
C_{max} (ng/mL)	2.11 (32.4) [n=12]	1.43 (75.9) [n=12]	0.68 (0.51-0.91)
AUC_{∞} (ng·hr/mL)	48.8 (26.9) [n=12]	132 (56.6) [n=12]	2.70 (2.16-3.38)
AP32960–to–TAK-788 molar AUC_{∞} ratio	0.473 (28.3) [n=12]	0.151 (68.4) [n=12]	-
$t_{1/2z}$ (hr)	28.2 (14.9) [n=12]	69.0 (26.7) [n=12]	-
AP32914			
t_{max} (hr)	6.00 (2.00-8.00) [n=9]	8.00 (6.00-12.00) [n=8]	-
C_{max} (ng/mL)	0.345 (49.2) [n=9]	0.215 (28.3) [n=8]	0.57 (0.46-0.70)
AUC_{∞} (ng·hr/mL)	7.16 (28.6) [n=5]	18.7 (27.9) [n=6]	2.61 (1.76-3.86)
AP32914–to–TAK-788 molar AUC_{∞} ratio	0.0615 (29.4) [n=5]	0.0205 (25.0) [n=6]	-
$t_{1/2z}$ (hr)	10.8 (31.3) [n=5]	53.4 (17.8) [n=6]	-
Combined Molar Exposure			
C_{max} (nM)	13.7 (30.7) [n=12]	39.2 (21.1) [n=12]	2.86 (2.48-3.30)
AUC_{∞} (hr·nM)	298 (35.2) [n=8]	1820 (18.0) [n=10]	6.27 (5.20-7.56)

AUC∞: area under the concentration-time curve, from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; CI: confidence interval; Cmax: maximum observed plasma concentration; LS: least-squares; PK: pharmacokinetic; t1/2z: terminal disposition phase half-life; tmax: time of first occurrence of Cmax A linear mixed effect model on the natural log-transformed parameters was performed with treatment as a fixed effect and subject as a random effect. The least squares means and difference of least squares means for the log-transformed parameters were exponentiated to obtain the point estimates and 90% CIs of the geometric LS mean ratio on the original scale. The statistical analysis was performed on Cmax and AUC∞ parameters only.
Treatment A: 20 mg TAK-788 (1 x 20 mg) administered at Hour 0 on Day 1 following an overnight fast.
Treatment B: 200 mg itraconazole oral solution administered every 24 hours for 14 consecutive days (within ±1 hour of Day 1 dosing) with a single dose of 20 mg TAK-788 administered at Hour 0 on Day 5 following an overnight fast.
a Parameters are presented as geometric mean (geometric mean %CV) [n], except for tmax, which is presented as median (range).
b The geometric LS mean ratio is calculated for Cmax and AUC∞ parameters only.
Source: Clinical Study Report TAK-788-106; Table 11.j pg. 67/99
TAK-788

Following administration of 200 mg itraconazole + 20 mg TAK-788, the geometric mean systemic exposure to TAK-788 (Cmax and AUC_{∞}) were greater compared to the corresponding values following 20 mg TAK-788 alone. The median tmax was reached approximately 2 hours later following 200 mg itraconazole + 20 mg TAK-788 compared to 20 mg TAK-788 alone. The geometric mean $t_{½z}$ was longer following 200 mg itraconazole + 20 mg TAK-788 compared to 20 mg TAK-788 alone.

Based on the statistical comparisons of ln-transformed PK parameters, the plasma TAK-788 C_{max} and AUC_{∞} following 200 mg itraconazole + 20 mg TAK-788 were approximately 383% and 843% of the

corresponding values obtained following 20 mg TAK-788 alone, which is >30% increase in exposure to TAK-788 defined in the protocol as a clinically significant DDI. The 90% confidence intervals (CIs) of the ratios of LSMs derived from the analyses on the ln-transformed Cm_{ax} and AUC_{∞} were outside the bioequivalence range of 0.80-1.25.

Combined molar plasma TAK-788, AP32960, and AP32914

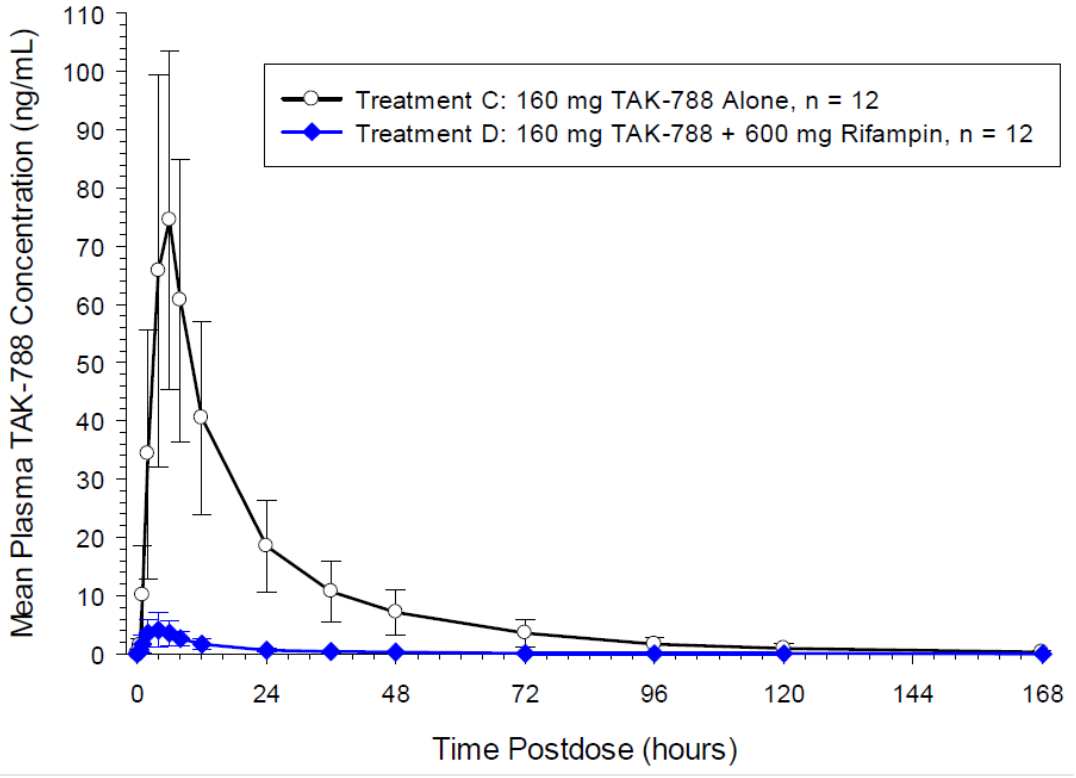
Based on the statistical comparisons of ln-transformed combined molar PK parameters, the plasma TAK-788, AP32960, and AP3214 combined molar C_{max} and AUC_{∞} following 200 mg itraconazole + 20 mg TAK-788 were approximately 286% and 627% of the corresponding values obtained following 20 mg TAK-788 alone, which is also >30% increase in combined molar exposure to TAK-788, AP32960, and AP32914 specified in the protocol as a clinically significant DDI. The 90% CIs of the ratios of LSMs derived from the analyses on the ln-transformed C_{max} and AUC_{∞} were outside the bioequivalence range of 0.80-1.25.

CYP3A4 Inducers

The study design of clinical DDI study TAK-788-1006 investigating also the effect of a strong CYP3A4 inducer (rifampin) on the PK of mobocertinib is described in the subsection CYP3A4 inhibition above.

The study results indicate a significant drug interaction between mobocertinib and rifampin after co-administration of multiple doses of rifampin:

Figure pk 5. Arithmetic Mean (SD) Plasma TAK-788 Concentration-Time Profiles Following Administration of a Single Oral Dose of 160 mg TAK-788 Alone (Treatment C) and Coadministration of Multiple Oral Doses of 600 mg Rifampin QD with a Single Oral Dose of 160 mg TAK-788 (Treatment D) in Healthy Subjects (Linear Scale) (PK Set) (Part 2)



Source: Clinical Study Report TAK-788-106; Figure 11.g pg. 70/99

The plasma TAK-788 profiles were generally well characterized in Part 2 following both treatments. Plasma TAK-788 concentrations were detectable in all subjects by 1 and 2 hours following 160 mg TAK-788 alone and 600 mg rifampin + 160 mg TAK-788, respectively.

Plasma TAK-788 concentrations remained quantifiable in the majority of subjects through the entire sampling interval (168 hours) following 160 mg TAK-788 alone and through 48 hours following 600 mg rifampin + 160 mg TAK-788. Peak mean plasma TAK-788 concentrations were reached at approximately 6 and 4 hours following 160 mg TAK-788 alone and 600 mg rifampin + 160 mg TAK-788, respectively. The mean concentrations of TAK-788 were higher throughout the entire sampling interval when 160 mg TAK-788 was administered alone compared to when 160 mg TAK-788 was administered with 600 mg rifampin.

Table pk 27. Plasma Pharmacokinetic Parameters of TAK-788 and Its 2 Active Metabolites AP32960 and AP32914 Following Coadministration of Multiple Oral Doses of 600 mg Rifampin QD with a Single Oral Dose of 160 mg TAK-788 (Treatment D) Versus Administration of a Single Oral Dose of 160 mg TAK-788 Alone (Treatment C) in Healthy Subjects (Part 2)

Parameter (unit)	TAK-788 alone [a] (Reference)	TAK-788 + Rifampin [a] (Test)	Geometric LS Mean Ratio (90% CI) (Test/Reference) [b]
TAK-788			
t_{max} (hr)	6.00 (4.00-8.00) [n=12]	4.00 (1.03-6.00) [n=12]	
C_{max} (ng/mL)	70.0 (42.5) [n=12]	3.65 (68.6) [n=12]	0.05 (0.04-0.07)
AUC_{∞} (ng·hr/mL)	1360 (51.0) [n=12]	56.9 (57.7) [n=11]	0.04 (0.03-0.05)
$t_{1/2z}$ (hr)	27.6 (17.5) [n=12]	19.5 (30.6) [n=11]	
AP32960			
t_{max} (hr)	6.00 (2.01-6.00) [n=12]	2.00 (1.03-6.00) [n=12]	
C_{max} (ng/mL)	29.6 (20.3) [n=12]	4.79 (66.4) [n=12]	0.16 (0.12-0.21)
AUC_{∞} (ng·hr/mL)	681 (31.2) [n=12]	55.8 (64.4) [n=11]	0.08 (0.07-0.10)
AP32960–to–TAK-788 molar AUC_{∞} ratio	0.514 (23.4) [n=12]	1.00 (11.9) [n=11]	
$t_{1/2z}$ (hr)	37.3 (20.5) [n=12]	22.9 (20.9) [n=11]	
AP32914			
t_{max} (hr)	6.00 (4.00-6.01) [n=12]	4.00 (1.03-119.92) [n=8]	
C_{max} (ng/mL)	2.29 (41.9) [n=12]	0.279 (55.5) [n=8]	0.12 (0.09-0.16)
AUC_{∞} (ng·hr/mL)	45.2 (53.9) [n=12]	3.59 (51.9) [n=5]	0.06 (0.04-0.08)
AP32914–to–TAK-788 molar AUC_{∞} ratio	0.0341 (16.5) [n=12]	0.0437 (7.1) [n=5]	
$t_{1/2z}$ (hr)	16.9 (34.2) [n=12]	6.76 (22.6) [n=5]	
Combined Molar Exposure			
C_{max} (nM)	177 (34.1) [n=12]	14.9 (68.0) [n=12]	0.08 (0.07-0.11)
AUC_{∞} (hr·nM)	3610 (43.2) [12]	194 (70.2) [n=9]	0.05 (0.04-0.07)

AUC∞: area under the concentration-time curve, from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; CI: confidence interval; Cmax: maximum observed plasma concentration; LS: least-squares; PK: pharmacokinetic; t1/2z: terminal disposition phase half-life; tmax: time of first occurrence of Cmax.

A linear mixed effect model on the natural log-transformed parameters was performed with treatment as a fixed effect and subject as a random effect. The least squares means and difference of least squares means for the log-transformed parameters were exponentiated to obtain the point estimates and 90% CIs of the geometric LS mean ratio on the original scale. The statistical analysis was performed on C_{max} and AUC_{∞} parameters only.

Treatment C: 160 mg TAK-788 (4 x 40 mg capsules) administered at Hour 0 on Day 1 following an overnight fast.

Treatment D: 600 mg rifampin (2 x 300 mg capsules) administered every 24 hours for 13 consecutive days (within ±1 hour of Day 1 dosing) with a single dose of 160 mg TAK-788 (4 x 40 mg) capsule administered at Hour 0 on Day 7 following an overnight fast.

a Parameters are presented as geometric mean (geometric mean %CV) [n], except for tmax, which is presented as median (range).

b The geometric LS mean ratio is calculated for Cmax and AUC∞ parameters only.

Source: Clinical Study Report TAK-788-106; Table 11.r pg. 80/99

TAK-788

Following administration of 600 mg rifampin + 160 mg TAK-788, the geometric mean plasma TAK-788 Cmax and AUC_{∞} were lower compared to the corresponding values following 160 mg TAK-788 alone. The median t_{max} was reached approximately 2 hours earlier, and the geometric mean $t_{½z}$ was shorter, following 600 mg rifampin + 160 mg TAK-788 compared to 160 mg TAK-788 alone.

Based on the statistical comparisons of ln-transformed PK parameters, the plasma TAK-788 C_{max} and AUC_{∞} following 600 mg rifampin + 160 mg TAK-788 were approximately 5% and 4% of the corresponding

values obtained following 160 mg TAK-788 alone, which is >25% loss in TAK-788 exposure referred to in the protocol as a clinically relevant DDI. The 90% CIs of the ratios of LSMs derived from the analyses on the ln-transformed C_{max} and AUC_{∞} were outside the bioequivalence criteria of 0.80-1.25

Combined molar plasma TAK-788, AP32960, and AP32914

Based on the statistical comparisons of ln-transformed combined molar PK parameters, the plasma TAK-788, AP32960, and AP32914 combined molar Cmax and AUC_{∞} following 600 mg rifampin + 160 mg TAK-788 were approximately 8% and 5% of the corresponding values obtained following 160 mg TAK-788 alone, which is >25% loss in combined molar exposure to TAK-788, AP32960, and AP32914 referred to in the protocol as a clinically relevant DDI. The 90% CIs of the ratios of LSMs derived from the analyses on the ln-transformed Cmax and AUC_{∞} were outside the bioequivalence criteria of 0.80-1.25.

Transporter

The potential of mobocertinib to interact with transporters has not been investigated in clinical studies.

3.3.1.2. Pharmacodynamics

The CSR of study AP32788-15-101 states the following regarding "biomarker results"

AP32788-15-101 Part 1 and 2 Biomarker Results

Next generation sequencing (NGS) analysis for cohorts dedicated to companion diagnostic submission will be reported as part of the submission for the companion diagnostic dossier for the EGFR exon 20 insertion mutation population. NGS panels are also able to report mutations in other genes including HER2.
Descriptive reporting of the genes read in liquid biopsy or tumor biopsy panels will be reported separately by the first quarter of 2022 or earlier. Circulating biomarkers including inflammatory biomarkers are currently being analyzed, and exploratory and descriptive analysis will be reported within 2 years of clinical read-out.

AP32788-15-101 Part 3 Biomarkers

Tumor DNA sequencing data were collected retrospectively, and the presence of EGFR exon 20 insertion mutation contributed to the confirmed population efficacy analysis.

Other detected mutation alterations in EGFR or in other genes will be assessed as modifiers of efficacy response and reported separately. Genetic data will be provided by the sequencing read of the NGS companion diagnostic in vitro device and comparator NGS test at time of unblinding for clinical validation. Biomarkers such as genetic alterations of circulating tumor DNA or circulating proteins will be determined after the last database lock and examined for potential association to efficacy and safety endpoints. Data will be reported separately by the first quarter of 2022 or earlier.

The future plans for the analysis and reporting of the exploratory biomarkers have been summarised as follows:

At time of this document, biomarker analysis was only partially completed and therefore is not included in this report. Tumor specimens are being analyzed for specific gene alterations with NGS panels for both DNA and RNA. The analysis will be focused on the presence of the type of EGFR exon 20 insertion mutations and co-occurring alterations in either the EGFR gene itself or other genes included in the panels to understand their impact in the response to mobocertinib. In addition, the analysis will support the companion diagnostic claim of well validated assays to be used in the clinics if mobocertinib demonstrates valuable efficacy in the patients with EGFR exon 20 insertion–mutated NSCLC. Plasma will also be analyzed with NGS with multiple objectives:

(1) Link the detection of altered EGFR in the plasma versus the tissue detection;
(2) Monitor the variant frequency variation over time and investigate the correlation between the measured molecular modulation of mutant frequency in the plasma with the observed clinical response as determined with the RECIST criteria.

In addition, circulating proteins linked with inflammation will be measured in plasma or serum to investigate a possible association with observed safety findings. Findings of these studies will be reported separately.

An E-R analysis was performed using applicable data from Study AP32788-15-101 (Exposure-Response Report). A concentration-QTc analysis was performed using time-matched PK and triplicate ECG data from Parts 1 and 2 of Study AP32788-15-101 (Concentration-QTc Report).

Exposure-response analyses

Exposure metrics (i.e. combined molar exposure) included both time-variant and early, time-invariant exposures: TAE (time-averaged exposure) and NDE (normalised daily exposure), and AUC on C1D1 (single dose) and on C2D1 (steady state) derived for each patient based on available dosing information and individual estimated PK parameter values predicted by the final popPK model.

In the E-R analyses for efficacy, combined molar exposure metrics were not statistically significant predictors of best confirmed clinical response or longitudinal efficacy data as assessed by the IRC, indicating that the efficacy benefit of mobocertinib was consistent across the observed range of exposures achieved after administration of 160 mg QD mobocertinib to patients with metastatic NSCLC with EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy and were enrolled in Parts 1, 2, or 3 of Study 101.

In the E-R analyses for safety including data from 295 patients enrolled in Parts 1, 2, or 3 of Study 101 who received mobocertinib doses ranging from 5 mg to 180 mg QD, combined molar (time-averaged) exposure was a statistically significant predictor of diarrhea, rash, stomatitis, and vomiting. Also, exposure was a statistically significant predictor of time to first mobocertinib dose reduction or interruption (whichever occurred first), with higher exposures associated with an increased risk for a dose reduction/interruption. These findings support the proposed dose reduction recommendations in the SmPC for patients experiencing treatment-emergent toxicities.

Mechanism of action

Mobocertinib (formerly TAK-788, AP32788) is an orally administered, irreversible tyrosine kinase inhibitor (TKI) that inhibits all activated forms of the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), including exon 20 insertion mutations. Mobocertinib forms a covalent bond with cysteine 797 in EGFR, which results in increased selectivity, sustained inhibition of EGFR signaling, and enhanced potency for mutant EGFR over wild-type (WT) EGFR according to the applicant.

Mobocertinib has two active metabolites, AP32960 and AP32914, which are found at approximately 62% and 7% of parent mobocertinib systemic exposure, respectively, and have similar activity to mobocertinib in kinase and cellular assays. Other examined metabolites had a low potency for inhibitory activity compared to mobocertinib as shown in an exon 20 cell viability model (metabolites M70, M108 were 72 and 3.4 times less potent, respectively), or as expected from the biotransformation pathways (metabolites M106 and M107).

The rationale to investigate mobocertinib in patients with NSCLC was outlined in the introduction of the Exposure–Response report as follows:

Mobocertinib (formerly TAK-788, AP32788) is a potent, selective inhibitor of mutant epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) and is an experimental oral drug in development for the treatment of patients with non-small cell lung cancer (NSCLC) harboring EGFR Exon 20 insertion mutations [2]. EGFR and HER2 are members of the HER/ERBB receptor tyrosine kinase family, which mediate cell proliferation and survival through downstream MAPK and PI3K pathways [3].Dysregulation or pathologic over-activation of EGFR and/or HER2 signaling, caused by activating gene mutations or gene amplifications, plays a causal role in a subset of NSCLC. There are several subtypes of EGFR mutations, but the two most common, Exon 21 substitution L858R and Exon 19 deletion (del19), are found in 90% of patients with NSCLC and are also the most closely associated with robust response to therapy[3]. An additional class of EGFR activating mutations, known as exon 20 insertions, comprise approximately 9% of cases.At the time of submission, no targeted therapies are approved for patients with exon 20 insertions or other uncommon EGFR mutations. HER2 mutations, typically consisting of in-frame insertions in exon 20, have also been identified as potential oncogenic drivers in 2% to 4% of NSCLC patients. There are presently no approved therapies for HER2 mutant NSCLC patients. Mobocertinib is being developed to address the limitations of existing therapies targeting EGFR and HER2 mutations. AP32914 and AP32960 were 2 human circulating metabolites of mobocertinib formed via CYP3A and were shown to be pharmacologically active with similar inhibitory activities to that of mobocertinib for EGFR and HER2[2].

Primary and Secondary pharmacology

Primary pharmacology

At the time being, pharmacodynamics of mobocertinib are mainly investigated in non-clinical studies and no dedicated primary pharmacodynamic study has been submitted.

Secondary pharmacology

The effect of mobocertinib on the heart rate corrected QT interval (Fridericia's method) (QTcF) was evaluated using time-matched PK and triplicate electrocardiogram (ECG) data from 194 patients with advanced malignancies enrolled in Parts 1 and 2 of Study AP32788-15-101 that received total daily doses of 5 to 180 mg mobocertinib. Linear mixed effects models were able to adequately describe the observed data and were able to predict drug-induced changes from baseline in QTcF.

Five concentration metrics (i.e. mobocertinib, AP32960 and AP32914, their molar sum and their estimated weighted sum) were evaluated as predictors of observed QTcF interval data. The estimated weighted sum was selected as the predictor of the exposure effect based on overall model fit.

Mobocertinib, AP32960 and AP32914, and their molar sum, yielded similar relationships between the concentration predictor and QTcF interval prolongation. The model included fixed effects to correct for the effect of time. The concentration-QTcF analysis suggested a statistically significant concentration-dependent increase in QTcF regardless of which exposure predictor was applied. At the steady-state Cmax following 160 mg QD doses of mobocertinib, the model predicted a QTcF interval change from baseline of approximately 12.7 msec (90% CI: 8.69, 16.8). There was no statistically significant relationship between concentration and the model-predicted RR interval, thereby supporting the lack of a clinically meaningful effect of mobocertinib on heart rate. As a result, concomitant use of mobocertinib with drugs known to prolong the QTc interval may increase the risk of QTc prolongation.

[2] Global Investigator's Brochure TAK-788 (AP32788), Edition 4. Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, 2020
[3] D. Morgensztern et al., Molecularly Targeted Therapies in Non-Small Cell Lung Cancer Annual Update 2014, vol. 10, no. 1 0 1. 2015

3.3.2. Discussion on clinical pharmacology

Bioanalytical methods

In the phase I study TAK-788-1001 and phase 1/2 study AP32788-15-101, Mobocertinib (AP32788 alias TAK-788) and both metabolites AP32960 and AP32914 concentrations were determined by RP-HPLC-MS/MS (ESI, MRM) using $^{2}H_5$ - internal standards in human plasma. In study TAK-788-1001 the analytes have also been determined in human urine samples.

For study TAK-788-1001 the bioanalytical method has been sufficiently described and validated.

Study AP32788-15-101 has been conducted at different sites in the US and in China.

Pharmacokinetics

The objective of the clinical pharmacology program was to describe the PK of mobocertinib and its 2 two active metabolites, AP32960 and AP32914, after oral administration.

Intrinsic and extrinsic factors that may affect the clinical pharmacology of mobocertinib were assessed either by prospectively designed clinical pharmacology studies or by population PK and PBPK analyses of the PK data collected from clinical studies across the development program.

The initial dose escalation portion of Study AP32788-15-101 (Part 1) investigated mobocertinib total daily doses from 5 to 180 mg. The maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) was determined to be 160 mg QD, and this dosage was evaluated in Part 2 and Part 3 of Study AP32788-15-101. Single doses from 20 to 160 mg mobocertinib were evaluated in the healthy subject studies.

All of the clinical studies were (or are being) conducted with immediate-release oral capsules except for Study TAK-788-1002, in which a microdose IV injection and an oral solution were also used. Mobocertinib capsules are an immediate-release oral dosage form containing mobocertinib drug substance as a "drug in capsule" ("DiC") with no excipients. One formulation of mobocertinib DiC, differing in the manufacturing process used to prepare the drug substance (i.e., Process A, B, and C, see drug substance part of the Quality AR for details) and 3 dose strengths (5 mg, 20 mg, and 40 mg), was used during the clinical development of mobocertinib. One dose strength (40 mg) of mobocertinib DiC-C in a size 1 capsule has been used in the phase 2 pivotal extension phase of clinical Study AP32788-15-101 Part 3. The commercial product will be DiC-C in a size 2 capsule.

To support the claim for bioequivalence between the drug products used during clinical development (DiC-A, -B and -C) and the one intended for marketing (DiC-C), the applicant has presented the clinical study 1001 part 3 (demonstrating bioequivalence between DiC-A and -B), quality data including dissolution investigations, popPK and PBPK modelling analyses. It is agreed that the totality of data indicate no effect of drug product on mobocertinib PK, and none is expected considering the nature of the drug product (DiC). Question raised concerning particle size specifications in the drug product intended for marketing compared to batches used to assess bioavailability have been assessed in the Quality AR (see there).

The geometric mean exposure ratio (oral/IV) for mobocertinib dose-normalized $AUC_{0-\infty}$ as the measure of absolute bioavailability (90% CI) was 36.7% (22.4 – 60.2%). The absorption section of the SmPC should be concisely amended, outlining that Mobocertinib has a high fraction absorbed of 91.7% but first-pass metabolism by CYP3A results in a lower absolute oral bioavailability of 36.7% (**OC**).

In study TAK-788-1001 in healthy volunteers, after single oral dose administration of mobocertinib, geometric mean plasma mobocertinib C_{max} ranged from 3.22 ng/mL at 20 mg to 52.2 ng/mL at 160 mg. The median t_{max} was 4.00 to 6.00 hours across this dose range. The geometric mean AUC_{∞} values

ranged from 63.6 h*ng/ml to 1020 h·ng/mL. Intersubject variability (%CV) for mobocertinib ranged from 28.2% to 66.1% for C_{max} and from 11.1% to 66.0% for AUC_{∞}.

After single oral dose administration of 160 mg mobocertinib (daily dose to be administered according to the current SmPC), the geometric mean plasma mobocertinib AUC_{∞} and C_{max} in healthy volunteers was 1020 h*ng/ml and 52.2 ng/mL, respectively. The median (range) t_{max} was 4.00 h (4.00 h - 6.00 h). For the active metabolites, the geometric mean plasma AP32914 AUC_{∞} and C_{max} were 85.2 h*ng/ml and 4.05 ng/mL, respectively (median (range) t_{max} was 6.00 h (4.00 h - 6.00 h)) and the geometric mean plasma AP32960 AUC_{∞} and C_{max} were 548 h*ng/ml and 25.4 ng/mL, respectively (median (range) t_{max} was 5.00 h (4.00 h -6.00 h)). The t_{max} in the range of 4.00 h - 6.00 h values indicate rapid metabolisation to the active metabolites.

In clinical study TAK-788-1002 Part 1, following a single oral dose of 160 mg mobocertinib in 6 healthy adult male subjects, the geometric mean plasma C_{max} values were 56.7, 23.3, and 4.09 ng/mL, and the geometric mean plasma AUC_{∞} values were 1050, 478, and 73.0 ng*h/mL for mobocertinib, AP32960, and AP32914, respectively. The median t_{max} values of mobocertinib and the main metabolites AP32960 and AP32914 ranged from 4.50 to 5.00 hours postdose. The results after a single oral dose administration of 160 mg mobocertinib are therefore in line with the results of study TAK-788-1001.

PK in subjects with Non-Small Cell Lung Cancer was investigated as part of clinical study AP32788-15-101. After single and multiple doses of 5 to 180 mg mobocertinib, mobocertinib was rapidly absorbed with a median tmax of approximately 4 h. This is similar to the 4-6 hours found in studies TAK-788-1001 and TAK-788-1002 in healthy volunteers. Four hours is the time stated for tmax in the SmPC, which is therefore adequately justified. The mean Cmax and AUC0-24 was 77.9 ng/ml and 972 ng*h/ml after single doses of 160 mg mobocertinib at Cycle 1 Day 1, respectively. At steady state at Cycle 2 Day 1, mean Cmax,ss and AUC0-24,ss was 70.4 ng/ml and 951 ng*h/ml, respectively which is very similar. After single doses of 160 mg mobocertinib at Cycle 1 Day 1, maximal Cmax values were found to be 365 ng/ml. The maximal AUC24 values was found to be 3970 ng*h/ml.

Like its parent compound mobocertinib, the median tmax of AP32960 was observed at approximately 4 hours after the QD dose on both Cycle 1 Day 1 and Cycle 2 Day 1. AP32960 AUC24 and Cmax on Cycle 1 Day 1 and Cycle 2 Day 1 increased in a dose-proportional manner over the mobocertinib dose range of 5 to 180 mg QD. In the dose range of 20 to 160 mg mobocertinib QD, the ratio of AP32960 molar AUC24 to mobocertinib molar AUC24 at C1D1 was in a range of approximately 0.3-0.5 and the ratio of AP32960 molar AUC24 to mobocertinib molar AUC24 at C2D1 was in a range of approximately 0.3-0.7. For the second metabolite, the ratio of AP32914 molar AUC24 to mobocertinib molar AUC24 at C1D1 was in a range of approximately 0.06-0.10 and the ratio of AP32914 molar AUC24 to mobocertinib molar AUC24 at C2D1 was in a range of approximately 0.05-0.10. It is therefore not agreed that the ratio was consistently shown to be "generally comparable". However, these results are based on a very low number of patients in the majority of dose groups and no trends, e.g. for ascending doses, can be seen. This issue will therefore not be further pursued.

The results of study AP32788-15-101 discussed above represent the basis for the following general PK information stated in section 5.2 of the SmPC: In patients receiving 160 mg mobocertinib once daily, the geometric mean (% coefficient of variation) steady-state C_{max} for mobocertinib, AP32960, and AP32914 was 70.4 (54.8), 40.6 (44.5), and 4.96 (50) ng/mL, respectively. The corresponding AUC_{24} values at steady-state were 951 (53), 572 (43.1), and 68.1 (53.5) hr•ng/mL, respectively. The geometric mean (% coefficient of variation) C_{max} and AUC_{24} values at steady-state for the combined molar exposure of mobocertinib, AP32960, and AP32914 were 202 (48.8) nM and 2760 (47.8) hr•nM, respectively. The steady-state AUC_{24} of AP32960 and AP32914 was 61.6% and 7.33% of the AUC_{24} for mobocertinib. After single- and multiple-dose administration, combined molar C_{max} and AUC_{24} of

mobocertinib, AP32960, and AP32914 was dose-proportional over the dose range of 5 to 180 mg once daily (0.03 to 1.1 times the recommended dosage). The geometric mean accumulation ratio for AUC_{24} of mobocertinib after multiple-dose administration of 160 mg once daily was 1.03.

Based on the analysis provided above, the applicant´s conclusions that dose proportionality was observed over the dose range of 40 to 160 mg of TAK-788 can be agreed on for the single dose studies. As requested, dose proportionality following multiple doses (5-180 mg) was further discussed and justified the applicant´s D120 Response. Based on the provided discussion, the information in the SmPC on dose proportionality for combined molar exposure of mobocertinib, AP32960, and AP32914 after multiple-dose administration is now regarded to be adequately justified.

Accumulation of mobocertinib and metabolite AP32960 was less extensive for the higher dose strength. This was discussed by the applicant to may be caused by auto-induction of the apparent oral clearance of mobocertinib likely via induction of CYP3A. The trend for a less extensive accumulation seen for the higher doses was not apparent from the data presented for AP32914. As requested, the applicant further discussed pharmacokinetics time dependency and justified that PK parameters on Cycle 2 Day 1 (i.e., Day 29 of treatment) can be reasonably expected to be representative of steady-state parameters, considering the terminal disposition phase half-life of mobocertinib (i.e., geometric mean of approximately 20 hours at 160 mg in Study TAK-788-1001 Part 1) and the time course for enzyme induction. In addition, the requested comparison of the pre-dose PK results also including results after sparse sampling in the extension phase at later time points (C3D1, C4D1 and C5D1) has been provided. Predose concentrations of mobocertinib and its active metabolites on Day 1 of later cycles (i.e., Cycles 3, 4, and 5) were similar to those observed on Cycle 2 Day 1. It is agreed that these data are consistent with achievement of steady-state by Cycle 2 Day 1.

As requested, the applicant amended the SmPC to consistently highlight in which population the cited results were gained.

Food effects were investigated in TAK-788-1001, Part 2 and TAK-788-1005. The results of study TAK-788-1001, Part 2 support the conclusion that mobocertinib may be taken with or without food, as stated in the current draft SmPC. The effect of concomitant intake of a low-fat meal on the extent (AUC) and rate of absorption (C_{max}) of a 160 mg dose in 10 healthy subjects was minor with 90% CI for the PK parameters AUC_{∞} and C_{max} contained completely within the 80% to 125% equivalence limits.

The results of study TAK-788-1005 also support the conclusion that mobocertinib may be taken with or without food: The effect of concomitant intake of a high-fat meal on the extent (AUC) and rate of absorption (C_{max}) of a 160 mg dose in 14 (fasted 13) healthy subjects was minor with 90% CI for the PK parameter C_{max} contained completely within the 80% to 125% equivalence limits. The PK parameter AUC_{∞} was not completely contained within the 80% to 125% equivalence limits for mobocertinib, indicating possibly slightly higher absorption (22%). It is agreed with the applicant that this slight increase is not expected to have clinically meaningful effects, especially as the combined molar AUC_{∞} of mobocertinib, AP32960, and AP32914 was still completely contained within the 80% to 125% equivalence limits.

Available non-clinical data indicate that mobocertinib and its 2 active metabolites AP32960 and AP32914 are highly bound to human plasma proteins (99.3%, 99.5%, and 98.6%). Please be referred to the Assessment of the Non-Clinical Part of the Application for details on investigation of binding to plasma proteins.

Plasma protein binding was not yet investigated *in vivo* but it is planned to be investigated in subjects with organ impairment and matched healthy subjects with normal organ function in ongoing studies

TAK-788-1007 (severe renal impairment study) and TAK-788-1008 (moderate and severe hepatic impairment study), see below.

Limited amount of total radioactivity was characterised in the mass balance study due to covalent binding to plasma proteins according to the applicant. Reversibility of covalent binding has not specifically been investigated. The applicant concludes that the covalent binding of mobocertinib and metabolites to plasma proteins is likely irreversible based on no evidence of a multiphasic elimination phase and that the half-life of total radioactivity was broadly similar to the half-life of serum albumin. This has also been observed for similar medicinal products, such as osimertinib. If binding of mobocertinib and metabolites to plasma proteins is irreversible and excreted as such, this can be considered an additional elimination pathway for mobocertinib and the active metabolites. The SmPC section 5.2 ("Biotransformation/Elimination") should be amended accordingly (**OC**).

The applicant states that validity of bioanalytical assays is not affected by the covalent binding of mobocertinib and metabolites to plasma proteins. The pharmacological effects of mobocertinib and metabolites in human plasma would not be expected to include a contribution from drug and/or metabolite that is irreversibly bound to plasma proteins.

As covalently bound material is not pharmacologically active, the longer terminal half-life observed for total radioactivity is not relevant when determining the time period for contraceptive use after the end of treatment. However, the applicant is asked to justify or change the updated recommendation in 4.6 (recommended period for use of effective non-hormonal contraception following end of treatment in women) according to current guidelines (**OC**).

As outlined in more details in the absorption section above, the blood-to-plasma C_{max} and AUC_{∞} ratios for mobocertinib, AP32960, AP32914, and combined molar exposure ranged from approximately 0.7 to 1.2. It is agreed that this indicates that mobocertinib, AP32960, and AP32914 did not show preferential distribution into human whole blood over plasma.

The apparent volume of distribution of 53.3 L/kg in the SmPC is taken from the popPK Model analysis.

The results of mass balance study TAK-788-1002 indicate that faecal excretion is the major route of elimination, while urinary excretion is the minor elimination pathway: After oral administration of [^{14}C]-mobocertinib as an oral solution, 3.57% of the administered total radioactivity was recovered in the urine and 76.0% was recovered in the feces. Only 1.13% of the administered mobocertinib dose was recovered in the urine as unchanged mobocertinib, AP32960, and AP32914 combined. The presented combined data from urine and feces indicate that 91.7% of the administered dose was absorbed into systemic circulation.

A single-dose design was used in the mass balance study, but the results can be extrapolated to steady-state conditions according to the applicant. Based on the results from the *in vivo* midazolam study (weak net induction of CYP3A, the main metabolising enzyme), oral CL/F is not expected to be substantially different following multiple doses compared to single dose administration. The observed PK data for mobocertinib and active metabolites following single and multiple dosing were consistent with a net autoinduction. It can be concluded that adequate characterisation of elimination pathways and (extractable) circulating drug material has been achieved based on single-dose data. However, section 5.2 ("Biotransformation/Elimination") of the SmPC should be updated to reflect current knowledge in more detail. Specifically, information on the pharmacologically active metabolites (and others if deemed relevant) should be provided, including data on their exposure relative to parent. Also, it should be described that the majority of radioactivity was covalently bound to plasma proteins (**OC**).

There were nine circulating components identified in human plasma. According to the applicant, the activities of AP32960 and AP32914 were similar to that of mobocertinib.

It can be concluded that the examined metabolites had a low potency for inhibitory activity compared to mobocertinib as shown in an exon 20 cell viability model, or as expected from the biotransformation pathways. However, the referred data has not been submitted. Provided that the referred data from the exon 20 cell viability model is submitted, the issue may be considered resolved (**OC**).

In Study TAK-788-1002 Period 2 the geometric mean renal clearance for mobocertinib was 0.657 L/hr, which is approximately 0.608% of the CL/F from the popPK analysis. According to the results of Study TAK-788-1001, the geometric mean renal clearance of mobocertinib following a 160 mg single dose was 2.11 L/hr (2110 mL/h), which is approximately 1.95% of the CL/F estimate from the population PK analysis and agreed to be overall consistent with the results observed in Study TAK-788-1002. The results from TAK-788-1001 and TAK-788-1002 indicate that renal clearance plays only a minor role in the overall clearance.

Using 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. See Non-Clinical AR for the assessment of studies using rhCYPs to investigate the contribution of different CYPs to mobocertinib metabolism.

No discussion on consequences of possible genetic polymorphism for the main metabolising/conjugating enzymes were provided in the submitted documentation.

A population pharmacokinetic model was built, combined for the parent compound as well as the two metabolites. The popPK model was developed based on a total of 17639 PK observations (mobocertinib, AP32960, AP32914) from 110 healthy subjects and 317 patients included in studies **15-101**, **1001**, **1003** and **1006**. All three analytes were quantified simultaneously in these studies.

A 2-compartment model was found to best describe the concentration-time profiles of mobocertinib and metabolite AP32960, with a first-order absorption process with three transit compartments for mobocertinib, whereas a 1-compartment model was used to describe the profiles for AP32914. An enzyme compartment was added in which the production of enzyme was described by an Emax model dependent on the molar sum of mobocertinib, AP32960, and AP32914 concentrations. This was used to describe the auto-induction of CYP3A4.

Covariates investigated were age, body weight, gender, race (non-Asian vs Asian), laboratory values (albumin, CLCr, bilirubin, ASP, ALT), estimated GFR, smoking, drug product (A vs B/C). Healthy effect vs patients status was a prefdefined covariate in the base model, and this strategy is currently questioned as it could potentially obscure other covariate relationships (**OC**). No other covariates were found to significantly influence the PK of the three substances with the available dataset. Mild to moderate renal impairment (EMA classification of CLCr) and mild hepatic impairment (NCI-ODWG criteria) were not found to impact mobocertinib or metabolite PK in a sensitivity analysis. The applicant has also presented plots derived by individual estimated exposure which are useful for explorative covariate analysis, however conclusions on the extent of covariate effects should preferably be based on model-predicted covariate effects on exposure.

The popPK model has low to moderate regulatory impact as it is used to inform the SmPC with population PK parameter estimates and impact of covariates (age, gender, body weight, race, renal and hepatic impairment) on mobocertinib PK, and to generate individual exposure metrics for ER analysis.It is agreed that the popPK model is able to describe PK in the overall target population as demonstrated by a reasonable model fit to the observed data, and it is also considered sufficient for ER exercises. However, the Emax model on enzyme induction is likely not supported by sufficient data to adequately describe this effect, and is thus not considered robust to confidently predict CL across time. Further, the popPK model was not able to explain the moderate to high variability in PK observed for mobocertinib (and metabolites), and there is still a pending issue related to the covariate analysis. The

conclusions regarding covariates (which currently is only informed by popPK modelling analysis) are thus considered preliminary. The model should only be used for descriptive purposes.

For the population PK dataset, a NONMEM subject identification number was assigned to a subject for each period the subject was dosed, effectively considering two occasions within a subject as being two independent NONMEM IDs. However, based on a sensitivity analysis, this did not impact parameter estimates in a clinically relevant manner. The parameters mainly influenced were EC50 and Emax, further indicating that the auto-induction model is not very robust.

TAK-788-1003 was a Phase 1, open-label, multicenter, dose-escalation part of a Phase 1/2 study to evaluate the safety, tolerability and PK of mobocertinib in Japanese patients with locally advanced or metastatic NSCLC. The dose-escalation cohorts started with 40 mg QD and was to be followed by higher dose cohorts until an MTD was determined or 160 mg QD was confirmed to be safe and tolerable in Japanese patients. After single-dose administration (Cycle 1 Day 1), C_{max} and AUC_{24} of mobocertinib increased with increased dose-level of mobocertinib: geometric mean of C_{max} (Geo %CV) at 40 mg QD, 120 mg QD, and 160 mg QD were 15.40 ng/mL (76.1), 70.28 ng/mL (56.2), and 100.2 ng/mL (36.3), respectively, and geometric mean of AUC_{24} were 152.9 ng*h/ml (62.2), 858.1 ng*h/ml (60.3), and 1196 ng*h/ml (43.0), respectively.

After repeated doses (Cycle 2 Day 1), $C_{max,ss}$ and $AUC_{24,ss}$ of mobocertinib at 120 mg QD and 160 mg QD were higher compared with 40 mg, however, comparable or slightly decreased with dose-level between 120 mg and 160 mg QD: geometric mean of $C_{max,ss}$ (Geo %CV) at 40 mg QD, 120 mg QD, and 160 mg QD were 17.90 ng/mL (34.4), 106.2 ng/mL (39.4), and 90.00 ng/mL (18.4), and geometric mean of $AUC_{24,ss}$ (Geo %CV) were 214.8 ng*h/ml (29.9), 1195 ng*h/ml (50.1), and 1141 ng*h/ml (25.9), respectively.

PK parameters AUC, C_{max} and t_{max} after single or multiple doses of daily oral 160 mg mobocertinib in Japanese non–small-cell lung cancer (NSCLC) patients) were generally comparable to the PK parameters found in the mainly non-Asian population investigated in AP32788-15-101. Similar to the results found in AP32788-15-101, a decreased systemic exposure to mobocertinib after multiple doses of the 160 mg dose was found. This was explained by the applicant by a postulated autoinduction of the apparent oral clearance of mobocertinib via induction of CYP3A.

With regard to the active metabolite AP32960 and AP32914, PK parameters AUC, C_{max} and t_{max} after single or multiple doses of daily oral 160 mg mobocertinib in Japanese non–small-cell lung cancer (NSCLC) patients were also generally comparable to the PK parameters found in the mainly non-Asian population investigated in AP32788-15-101 (the differences were, however, somewhat more pronounced for AP32914).

Study 1003 part 1 included 20 Japanese patients, and PK data were included in the popPK dataset. In the pivotal study 101 15.8% (part 1/2, rich sampling) and 68.8% (part 3, sparse sampling) were Asians. The applicant was asked to further investigate the impact of race (based on NCA and popPK analysis). As discussed in detail in the Clinical AR, the effect of race on the PK of mobocertinib and its active metabolites was not a statistically significant covariate in the popPK analysis. Additionally, plots comparing model predicted exposures in Asians vs. non-Asians were presented as supportive information in the original submission. It is agreed that shrinkage for the overall model was acceptable, however, shrinkage is not model dependent, but rather depended on the dataset and may be different in sub-populations. Hence, individual predictions to conclude on extent of covariates effects should be viewed as exploration prior to testing of covariates by including them in the model. Considering the unexplained/observed differences in safety (e.g. QTc prolongation) between Asians and non-Asians, additional analysis of observed exposures in these groups were requested.
The applicant claim similarity in PK between Asians and non-Asians based on graphical comparison of intensive (C1D1 and C2D1) and sparse (trough on D1 of C2-5) PK data collected in study 101 (part 1

and 2) and study 1003 (part 1) following administration of mobocertinib 160 mg single and multiple dose. Geometric mean Cmax, AUC24 and Ctrough for mobocertinib, AP32960, AP32914, and combined molar sum are similar, but slightly higher for Asians compared to non-Asians. Variability is mostly overlapping. Preferably, also a tabulated comparison (e.g. geom mean, %CV, range) should have been presented.

Based on the above, it is agreed that PK of mobocertinib appear similar in non-Asians and Asians. However, considering the observed difference in safety between Asians and non-Asians, race should be tested as a covariate in the requested updated popPK model analysis. The current SmPC text is thus considered preliminary.The SmPC section 5.2 should be amended to include a relevant description of the popPK data set with respect to race (**OC**).

In the popPK analysis, hepatic function (normal vs mild impairment) or renal function (normal vs mild or moderate renal impairment) were not significant covariates on CL/F for mobocertinib, AP32960 or AP32914. Dedicated hepatic and renal impairment PK studies are not available until December 2022 and March 2023, respectively, and submission is not likely to be expected within the current procedure. The applicant should commit to submit the results from renal and hepatic impairment studies TAK-788-1007 and TAK-788-1008 as post-authorisation measures (**OC/PAM**). In the meantime, based on the discussion on safety risk associated with increasing mobocertinib concentrations discussed in depth in the Clinical AR and in line with exclusion criteria in the pivotal study, it seems necessary and adequate that mobocertinib should not be administered in patients with moderate or severe hepatic impairment or severe renal impairment. In consequence, the applicant is asked to amend sections 4.2 and 4.4 of the SmPC and PL (**OC**).

The applied indication is restricted to adults only and there is no relevant use of mobocertinib in the paediatric population in the treatment of NSCLC.

Non-clinical and clinical studies dedicated to investigate mobocertinib´s potential for drug-drug interaction showed that clinically relevant interactions on the level of CYP enzymes can be expected. The extent of potential drug interactions seems to be more pronounced for effects of other drugs on mobocertinib (as a victim) than for mobocertinib effects on other drugs (as a perpetrator).

With regard to mobocertinib as a perpetrator, mobocertinib CYP inhibition or induction has been investigated in clinical study TAK-788-1004. In this study the effect of mobocertinib on oral and IV midazolam PK was assessed in an ongoing fixed-sequence DDI study design. Statistical analysis comparing systemic exposures of midazolam after a single oral dose of midazolam coadministered with mobocertinib to oral midazolam alone resulted in geometric LS mean ratios (90% CI) for Cmax, AUClast and AUC∞ of 1.03 (0.739, 1.42), 0.740 (0.580, 0.943) and 0.676 (0.532, 0.859), respectively.

Similarly, statistical analysis comparing systemic exposures of midazolam after a single IV dose of midazolam coadministered with mobocertinib versus IV midazolam alone resulted in geometric LS mean ratios (90% CI) for Cmax, AUClast and AUC∞ of 1.30 (0.886, 1.92), 0.926 (0.723, 1.19) and 0.837 (0.673, 1.04), respectively.

Thus, mobocertinib increased oral midazolam Cmax by approximately 3% but decreased midazolam AUClast and AUC∞ by approximately 26% and 32%, respectively.

Additionally, mobocertinib increased IV midazolam Cmax by approximately 30% but decreased the AUClast and AUC∞ by approximately 7% and 16%, respectively.

The study design of study TAK-788-1004 is adequate to investigate the effect of concomitant mobocertinib administration on the CYP3A substrate midazolam. Overall, the study results are

adequately reflected in the SmPC section 4.5. It is agreed that the of decrease in oral and IV midazolam AUC∞ by 32% and 16%, respectively should be classified as mild. In line with the EMA DDI Guidance, the SmPC and PL should be amended to use the classification "mild inducer" instead of "weak inducer" as currently proposed (**OC**).

Section 4.5 of the SmPC also states: "*If coadministration is unavoidable, the CYP3A substrate dose should be increased in accordance with its approved Summary of Product Characteristics*". This general recommendation of dose increase with reference to the SmPC of other products is regarded not optimal, as measures to be taken for management of this interaction will be highly dependent of the medicinal product in question. In consequence, the applicant is asked to remove this sentence (**OC**).

Although mobocertinib is considered highly soluble across physiological pH range, *in vitro* dissolution data demonstrated increased variability in drug product dissolution rate and a decrease in dissolution rate with increased pH. At pH 1.2 to 6.5 85% the drug product was dissolved within 85 minutes, while at pH 6.8 ~70% was dissolved within 30 minutes (USP apparatus I, 100rpm). Dissimilarity was pronounced at investigated pHs 4.5-6.8. Concomitant use of PPIs was allowed during study 101 (part 1 and 2). Based on a graphical comparison, observed mean Cmax and AUC24 at C1D1 and C2D1 following administration of mobocertinib 160 mg QD were similar between patients receiving PPIs and those not receiving PPIs. It is agreed that coadministration of mobocertinib with acid-reducing medicinal products, such as PPIs, is not expected to impact the PK of mobocertinib through modulation of pH and that a clinical DDI study is not warranted.

Potential for inhibition of P-gp, BCRP and OCT1 in vivo cannot be excluded based on in vitro findings. Induction of P-pg is also possible based on the observed induction of CYP3A (co-regulated via PXR). The submitted PBPK analyses are not considered fit to conclude that there is a low potential for DDIs and should not inform the SmPC. Therefore, the SmPC should be updated accordingly, including appropriate warnings/information (**OC**). Further, the applicant should submit the in vivo BCRP study (requested by the FDA) when available (**OC/PAM**).

With regard to mobocertinib as a victim, Part 1 of Study TAK-788-106 showed that AUC_{∞} and C_{max} of mobocertinib were increased by 843% and 383%, respectively, when mobocertinib was co-administered with the strong CYP3A4 inhibitor itraconazole. T_{max} was only slightly affected by co-administration of itraconazole in this study (a median of 6 h compared to 8 h without and with concomitant itraconazole, respectively).The results for the combined molar PK parameters (mobocertinib, AP32960, and AP3214 combined) showed comparable strong effects of CYP3A4 inhibition with itraconazole as C_{max} and AUC_{∞} following 200 mg itraconazole + 20 mg mobocertinib were approximately 286% and 627% of the corresponding values obtained following 20 mg mobocertinib alone.

The applicant has used a PBPK model to predict the effect of strong, moderate and weak CYP3A inhibitors on mobocertinib as victim drug at steady state. The model is not considered fit for the intended purpose. Consequently, PBPK predictions (multiple dose) in section 4.5 should be removed while data from the clinical DDI study should be retained (single dose).

A complex PBPK model was developed for mobocertinib and the two metabolites including elimination via the kidney, additional systemic clearance, metabolism via CYP3A4, including auto-inhibition and auto-induction, and via CYP2B6, 2C8, 2C9, PGP and BCRP. With the available data, platform qualification according to the EMA PBPK guideline (EMA/CHMP/458101/2016) has not been shown. Interaction data between mobocertinib and itraconazole (strong CYP3A4 inhibitor) and midazolam as a substrate and mobocertinib as net CYP3A4 inducer have been used for model development, and data from the interaction study between mobocertinib and rifampicin (strong CYP3A4 inducer) have been used for model evaluation. The applicant has used a PBPK model to predict the effect of strong/moderate/weak CYP3A inhibitors and strong/moderate CYP3A inducers on mobocertinib as

victim drug at steady state. These predictions are considered to be of high regulatory impact as the approach concerns a waiver for confirmatory clinically studies on weak/moderate CYP3A inhibitors and moderate CYP3A inducers, and as the predictions inform the SmpC and are used to propose dose recommendations. The available databases on inhibition and induction are too limited to qualify the complex model for the intended purpose. As there is currently limited experience and low confidence in DDI predictions involving combined CYP3A inhibition and induction, predictions of the effects of CYP3A inhibition and induction on repeated dose mobocertinib are not accepted. This decision is also justified by a risk-based assessment. While the exposure-response relationship for efficacy and safety is to a large extent uncharacterised, the risk of serious adverse events, including QT prolongation, is expected to increase with increasing exposure. Hence, only a very limited level of uncertainty in model predictions can be accepted.

In response to questions raised in the initial assessment, the applicant revised the dosing recommendation language for strong CYP3A inhibitors in Section 4.5 of the SmPC by replacing "should be avoided" with "is not recommended."

In addition, the applicant has also updated the QTc Interval Prolongation subheading in Section 4.4 of the SmPC to note that CYP3A inhibitors should be avoided as they may increase the risk of heart-rate corrected (QTc) interval prolongation.

The newly proposed wording on strong inhibitors in section 4.5 is not perceived to be a significant improvement as it seems to even weaken the advice not to concomitantly administer strong CYP3A inhibitors.
The section should be amended to state that moderate (e.g., fluconazole and erythromycin) and strong CYP3A inhibitors (including but not limited to certain antivirals (e.g., indinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin, telithromycin, troleandomycin), antifungals (e.g., ketoconazole, voriconazole), and nefazodone) should not be used.

The requested amendments are justified as it is known that administration of concomitant cytochrome P450 CYP3A inhibitors can significantly increase the AUC (AUC∞ by 843% in TAK-788-1006) and that no safety information regarding concomitant administration of moderate or strong CYP3A inhibitors are available from the pivotal efficacy study 101.

Further, there seems to be a clear concentration-related effect on QT (see safety sectionand SmPC section 4.8). Hence, it seems necessary to strengthen the warning that strong and moderate CYP3A inhibitors should not be co-administered. Based on the requirements of the Protocol for study 101, strong and moderate CYP3A inhibitor should have been discontinued for 10 days or for 3 to 5 elimination half-live, whatever is longer, prior to first dose of mobocertinib. The applicant is asked to comment and revise the SmPC and PL as outlined above and in the Clinical AR (**OC**).

In the Response to D120 LoQ, the applicant further justified that the effect of CYP3A inhibitors on the steady-state PK of mobocertinib, AP32960, and AP32914 was evaluated using a PBPK modelling approach. It is acknowledged that a steady-state DDI study is probably not feasible in healthy volunteers due to the safety profile of mobocertinib. It is also acknowledged that conducting a DDI study in a rare cancer patient population is associated with significant challenges, especially pre-authorisation. However, the applicant is asked to comment on the possibility to further investigate effects of moderate CYP3A4 inhibitors and inducers with the proposed adjusted doses (half of the dose in concomitant administration with CYP3A moderate inhibitors and double the dose with moderate inducers) on steady-state PK in the patient population applied for in a post authorisation setting (**OC**).

With respect to concomitant use of CYP3A4 inducers, the applicant acknowledged the CHMP´s concern about increasing the dose above 160 mg QD based solely on the PBPK model and has thus removed this originally proposed dose adjustment text from Section 4.5, which is endorsed. The safety risks

potentially associated with an inappropriate increase of the mobocertinib dose are similar to the ones discussed above for DDIs with CYP3A inhibitors.

In addition, the applicant has proposed to amend Section 4.5 of the SmPC with PBPK model-informed recommendations for coadministration of strong and moderate CYP3A inducers given the potential for loss of efficacy. However, as the PBPK model is not considered adequately qualified, the clinical DDI data should be retained, while the PBPK predictions should be removed. The proposed wording for the strong inducers is not regarded to be a major improvement. The section should be amended to state that strong CYP3A inducers should not be used concomitantly with Exkivity. Based on the requirements of the Protocol for study 101, it seems as if strong and moderate CYP3A inducers should be discontinued for 10 days prior to first dose of mobocertinib. Additional data would be needed to define an appropriate dose in concomitant administration with moderate inducers.
To clearly inform about the potential negative effect on efficacy which can reasonably be expected after a significant reduction in mobocertinib concentrations due to concomitant administration of strong CYP3A inducers, the applicant is asked to revise all parts dealing with DDIs with strong and moderate CYP3A inducers of the SmPC and PL in line with the discussion above and proposal outlined in detail in the Clinical AR (**OC**).

Pharmacodynamics

At the time being, pharmacodynamics of mobocertinib are mainly investigated in non-clinical studies and no dedicated clinical pharmacodynamic study has been submitted. As outlined above, it is planned that results of e.g. next generation sequencing (NGS) analysis and liquid biopsy or tumor biopsy panels will be reported substantially later: Study AP32788-15-101 is an ongoing phase 1/2 Study and biomarker analysis, e.g. next generation sequencing (NGS) analysis and liquid biopsy or tumor biopsy panels as described in the introduction above, were only partially completed and not included in this report.

According to the EMA Template, PD studies assessed in this section are expected to be conducted at early stage of clinical development to, beside others, elucidate the mechanism of action, provide preliminary proof of concept (PoC) and to characterise the range of exposures or doses that are likely or not to have a therapeutic effect in patients and to be further investigated in dose ranging efficacy and safety trials.

These studies should also investigate covariate effects on primary pharmacology i.e. effects of age or genetic polymorphism on PK/PD relationships.

Especially early dose finding studies are particularly important, as they are aiming to describe the selection of doses for the confirmatory dose-response studies based on parameters of efficacy and tolerability in escalating dosing. The objective of these studies is normally the early understanding of the therapeutic width and to define the dose response of the product.

The applicant was asked to submit the results of available biomarker analysis or state when the results are expected to be available for assessment. No further results of biomarker analysis were provided, as according to the applicant mobocertinib was already well-characterized *in vitro* and *in vivo*.
The applicant referred to one publication by Gonzalvez et al in Cancer Discovery (Gonzalvez et al. 2021) where, beside others, mobocertinib was investigated in patient-derived tumor models harboring diverse EGFRex20ins mutations. As stated in the publication, all studies were funded by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.
The pre-/non-clinical findings published by Gonzalvez et al. and partly cited in the response were not further assessed in the clinical part as non-clinical results (beyond what was published by Gonzalvez et al.) have been assessed in the non-clinical part of the assessment. This point not be further pursued, the assessment will have to be based on the available non-clinical and clinical data.

The effect of mobocertinib on the heart rate corrected QT interval (Fridericia's method) (QTcF) was evaluated using time-matched PK and triplicate electrocardiogram (ECG) data from 194 patients with advanced malignancies enrolled in Parts 1 and 2 of Study AP32788-15-101 that received total daily doses of 5 to 180 mg mobocertinib. Linear mixed effects models were able to adequately describe the observed data and were able to predict drug-induced changes from baseline in QTcF. Goodness-of-fit plots revealed no systematic trends and VPCs showed acceptable performance of the C-QTc models. According to the ICH E14 "If not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure." The current analysis included only data up to a dose of 180mg, which is only minimally above the therapeutic dose of 160mg. It is considered that application of much higher doses is hampered by toxicity. And since even with this dose range a clear association of concentration-QTc was seen, this is considered acceptable. Overall, the C-QT analyses confirm the potential of mobocertinib and its metabolites to prolong QTc interval seen in the clinical trials. This risk needs to be adequately addressed in the SmPC, see new OCs raised demanding a strengthening of the warnings on potential DDIs and consequences of hepatic and renal impairment.

The SmPC currently submitted states as follows with regard to pharmacodynamic interactions with drugs that prolong the QTc interval: *"Coadministration of Exkivity with medicinal products known to prolong the QTc interval (e.g., anti-arrhythmic medicinal products, macrolide antibiotics, fluoroquinolones, triazole antifungals, 5 HT3 receptor antagonists) and moderate or strong CYP3A inhibitors may increase the risk of QTc interval prolongation. When feasible, avoid coadministration of medicinal products known to prolong the QTc interval with a risk of Torsades de Pointes. If coadministration of Exkivity with moderate CYP3A inhibitors or with medicinal products known to prolong the QTc interval is unavoidable, conduct periodic ECG monitoring (see section 4.4 and 5.1)."* It is agreed that QTc interval prolongation is a risk associated with the use of mobocertinib and the SmPC and PIL need to adequately cover all aspects related to that. Further SmPC amendements are warranted and OCs have been raised (see above).

Biomarker analysis was only partially completed and therefore not included in the submitted reports. Beside others, it was outlined that tumor specimens are being analysed for specific gene alterations with NGS panels for both DNA and RNA. The analysis will be focused on the presence of the type of EGFR exon 20 insertion mutations and co-occurring alterations in either the EGFR gene itself or other genes included in the panels to understand their impact in the response to mobocertinib. To better understand what further analyses are planned and which topics are covered, the applicant was asked to provide a dedicated discussion on possible consequences of genetic differences. The biomarker analysis results provided within the Response (publication by Zhou et al. 2021) are based on a (very) small number of patients in each group, no final conclusion on the impact of different EGFR exon 20 insertion variants on mobocertinib clinical efficacy can be drawn. The applicant is asked to comment on if and how the impact of different EGFR exon 20 insertion variants on mobocertinib clinical efficacy could be further investigated post authorisation (**OC**).

Updated exposure-efficacy analyses have been provided as requested in the D120 LoQ. Overall, the exposure-efficacy analyses did not identify a statistically significant relationship between exposure following administration of mobocertinib 160 mg QD and best confirmed clinical response or longitudinal clinical responses. This supports that comparable efficacy was achieved across the range of exposure achieved following the 160 mg dose. However, this only means that the efficacy was shown to be consistently at a higher or lower level, which, depending on the efficacy seen, does not necessarily translate into a benefit for the (majority) of patients, see efficacy assessment. Mobocertinib exposure-response relationship remains unknown regarding efficacy endpoints, and it is not possible to conclude regarding efficacy at a lower dose (e.g. 120 mg) based on these analyses.

In the ER analyses for safety (5 mg to 180 mg mobocertinib), positive associations between exposure and risk of adverse events (diarrhea, rash, stomatitis, and vomiting) and time to dose reduction/interruption were demonstrated supporting dose reduction recommendations due to AEs in the SmPC. Also, this indicates that an improved safety profile could potentially be achieved at a lower dose.

Standard MTD dose finding was used in study **101**, which is an obsolete and inappropriate strategy. Consequently, one cannot be confident that the most well-balanced dose with regards to efficacy and safety has been chosen. Further dose optimisation efforts are recommended (**OC**).

3.3.3. Conclusions on clinical pharmacology

Pharmacokinetics
Pharmacokinetic properties of mobocertinib have been overall adequately described. However, some aspects, some of them representing a serious safety concern if not adequately resolved, have to be further elucidated by the applicant. Aspects to be further discussed are, beside others, necessary warnings in the PI concerning concomitant intake of CYP3A4 inhibitors and inducers as well as hepatic and renal impairment (see LoQ).

Pharmacodynamics
At the time being, pharmacodynamic properties of mobocertinib are mainly investigated in non-clinical studies and no dedicated clinical pharmacodynamic study has been submitted.

The E-R relationships are not considered sufficiently investigated and the applicant is asked to comment on if and how dose-exposure-response relationships could be further investigated post authorisation. The applicant is also asked to comment on if and how the impact of different EGFR exon 20 insertion variants on mobocertinib clinical efficacy could be further investigated post authorisation (see LoQ).

3.3.4. Clinical efficacy

Table eff 2 tabular overview of pivotal study AP32788-15-101

No. of Sites-Country **Study Start-End Dates**	**Study Design** **Primary Objective (Endpoint)**	**Population a and Type (Criteria)** **Sex and Race (n [%])** **Mean Age (Min, Max)**	**Treatment Duration**	**Treatment (Enrolled/Completed)**
Parts 1 and 2: 28-US Part 3: 21-Asia (China, Japan, South Korea, Taiwan) 30-North America (US) 19-Europe (Germany, Spain, UK, Italy) Study ongoing since 08 June 2016	Part 1: Open-label, multicentre, dose escalation study (3 + 3 design with additional expansion) in patients with advanced NSCLC who are refractory to standard available therapies. Safety, PK, and RP2D. Part 2: Open-label, multicentre study with 7 histologically and molecularly defined cohorts of patients with advanced NSCLC or other solid tumours with EGFR or HER2 mutations. Antitumour activity. Part 3: Open-label, multicentre study with single arm extension cohort of patients with locally advanced or metastatic NSCLC harbouring EGFR exon 20 insertion mutations who have	Part 1: 73 patients with advanced NSCLC Part 2: 136 patients with advanced NSCLC or other solid tumours with EGFR or HER2 mutations. Parts 1 and 2 (209 patients): Male 66 (31.6), Female 143 (68.4) 154 (73.7) W, 33 (15.8) A, 14 (6.7) B, 5 (2.4) U, and 3 (1.4) O 61.4 (24, 86) years Part 3: 96 patients with locally advanced or metastatic NSCLC harbouring EGFR exon 20 insertion mutations. Male 34 (35.4), Female 62 (64.6) 66 (68.8) A, 28 (29.2)	Part 1: Total daily doses explored include 5, 10, 20, 40, 80, 120, 160, and 180 mg mobocertinib orally, continuously in 28-day cycles. Parts 2 and 3: 160 mg mobocertinib QD orally, continuously in 28-day cycles.	Part 1: mobocertinib (73 treated/63) Part 2: mobocertinib 160 mg QD (136 treated/83) Part 3: mobocertinib 160 mg QD (96 treated/45) (as of 01 November 2020)

	received at least 1 prior line of therapy for locally advanced or metastatic NSCLC. Efficacy (confirmed ORR, per IRC).	W, 2 (2.1) B 59.1 (27, 80) years		

Source: 'module 5.2 tabular listing of clinical studies'

3.3.4.1. Dose-response studies

The dose for registration (160 mg QD) is identical to the recommended phase 2 dose (RPD2D) investigated in Part 2 and 3 of Study AP32788-15-101, as according to the applicant this is the dose for which a favourable benefit/risk profile for the treatment of patients with previously treated NSCLC harbouring EGFR exon 20 insertion mutations has been seen.

The RPD2D selection was based on the maximum tolerated dose (MTD) as follows: The RP2D was the MTD or less. An RP2D less than the MTD may have been chosen if aspects of tolerability or efficacy not encompassed by the MTD determination suggested utilizing a lower dose.

In the CSR of Study TAK-788-15-101 the MTD and corresponding dose limiting toxicities (DLTs) were defined as follows:

MTD: The MTD was defined as the highest dose at which ≤1 of 6 evaluable patients experienced a dose limiting toxicities (DLT) within the first 28 days of treatment (end of Cycle 1). Evaluable patients must have completed at least 75% of their planned doses, unless missed doses were due to adverse events (AEs).

DLT: Dose limiting toxicities were summarized by category (hematologic and nonhaematologic) and by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT). Standard AEs were considered DLTs that counted for the determination of the MTD of mobocertinib. A DLT was a drug-related toxicity that was observed to occur within the first 28 days of treatment (end of Cycle 1) as defined below. Drug-related toxicities included any toxicity that was possibly, probably, or definitely drug related. Toxicity grades were defined by the NCI CTCAE v4.0 prior to Amendment 3 and by NCI CTCAE v5.0 following Amendment 3, if needed. DLTs were defined by the following:

- Nonhaematologic toxicities:

  - Any Grade ≥3 nonhaematologic toxicity, with the exception of self-limiting or medically controllable toxicities (eg, nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting <3 days, and excluding alopecia.

- Haematologic toxicities:

  – Febrile neutropenia not related to underlying disease (fever, >101°F [>38.3°C]; ANC $<0.5 \times 1^9$/L).

  - Prolonged Grade 4 neutropenia (≥7 days).

  - Neutropenic infection: Grade ≥3 neutropenia with Grade ≥3 infection.

  - Thrombocytopenia Grade ≥3 with bleeding or Grade 4 without bleeding lasting ≥7 days.

- Missed ≥25% of planed doses of mobocertinib over 28 days due to treatment-related AEs in the first cycle.

In January 2018, 160 mg QD was identified as the MTD based on the results of Part 1 (dose escalation phase). On the basis of the efficacy, safety, and PK results observed in Part 1 of this study, the decision was made to open Part 2 (phase 2 expansion cohorts) with 160 mg QD (defined as MTD) as the RP2D on 19 January 2018. Analysis supporting the early proof-of-concept assessment on the basis

of Parts 1 and 2 of the study was conducted in August 2018 and confirmed that 160 mg QD was also the RP2D for Part 3 (extension cohort; designed as a pivotal cohort).

The analysis of efficacy was based on the expanded refractory exon 20 cohort, defined as previously treated patients with NSCLC with EGFR exon 20 insertion mutations who received 160 mg QD in Part 1 and Part 2 Expansion Cohort 1 (21 patients had been enrolled at the time of August 2018 analysis). Analysis of the patients whose tumours harboured EGFR exon 20 insertion mutations at the 120 mg QD dosage also revealed promising clinical efficacy, but the ORR was lower at this dose (33.3%; N = 9) compared with 160 mg QD (47.6%; N = 21). This difference in ORR was considered clinically meaningful.

The corresponding preliminary emerging PK results showed a dose-proportional increase in drug exposure of mobocertinib combined with 2 active metabolites (AP32960 and AP32914) following a single dose of mobocertinib. However, steady-state exposures of mobocertinib following multiple dose administration increased less than dose-proportionally, with the exposure at 160 mg QD following multiple-dose treatment being comparable to 120 mg QD, which suggested autoinduction of the apparent oral clearance of mobocertinib at 160 mg QD. This potential autoinduction is likely explained by concentration-dependent induction of CYP3A by mobocertinib.

Although potential autoinduction was observed at 160 mg QD resulting in the lack of meaningful increase in steady-state exposures from 120 mg QD to 160 mg QD, 160 mg QD was considered as the RP2D based on the following rationale: 1) higher observed ORR; 2) comparable safety profile; and 3) given the high heterogeneity of EGFR exon 20 insertion mutations and their varied sensitivity to mobocertinib, 160 mg QD was predicted to achieve sufficient exposure to inhibit most EGFR exon 20 insertion mutations.

Because of the potential autoinduction, a reassessment of the RP2D was conducted after additional patients were added to the 120 mg QD cohort. Based on efficacy data extracted on 17 June 2019 from the expanded refractory exon 20 cohort and safety data from a data cut-off of 01 March 2019 in all patients treated with 160 mg QD or 120 mg QD in Parts 1 and 2. The reassessment confirmed 160 mg QD as the RP2D for Part 3 (the pivotal extension cohort) and as the recommended phase 3 dose for the phase 3 Study TAK-788-3001. The cORR by investigators at 160 mg QD (43%; N = 28) was notably higher compared with 120 mg QD (19%; N = 21), and the 160 mg QD dose had an acceptable safety profile; in general, there were no notable differences in the safety profile between 160 mg QD and 120 mg QD.

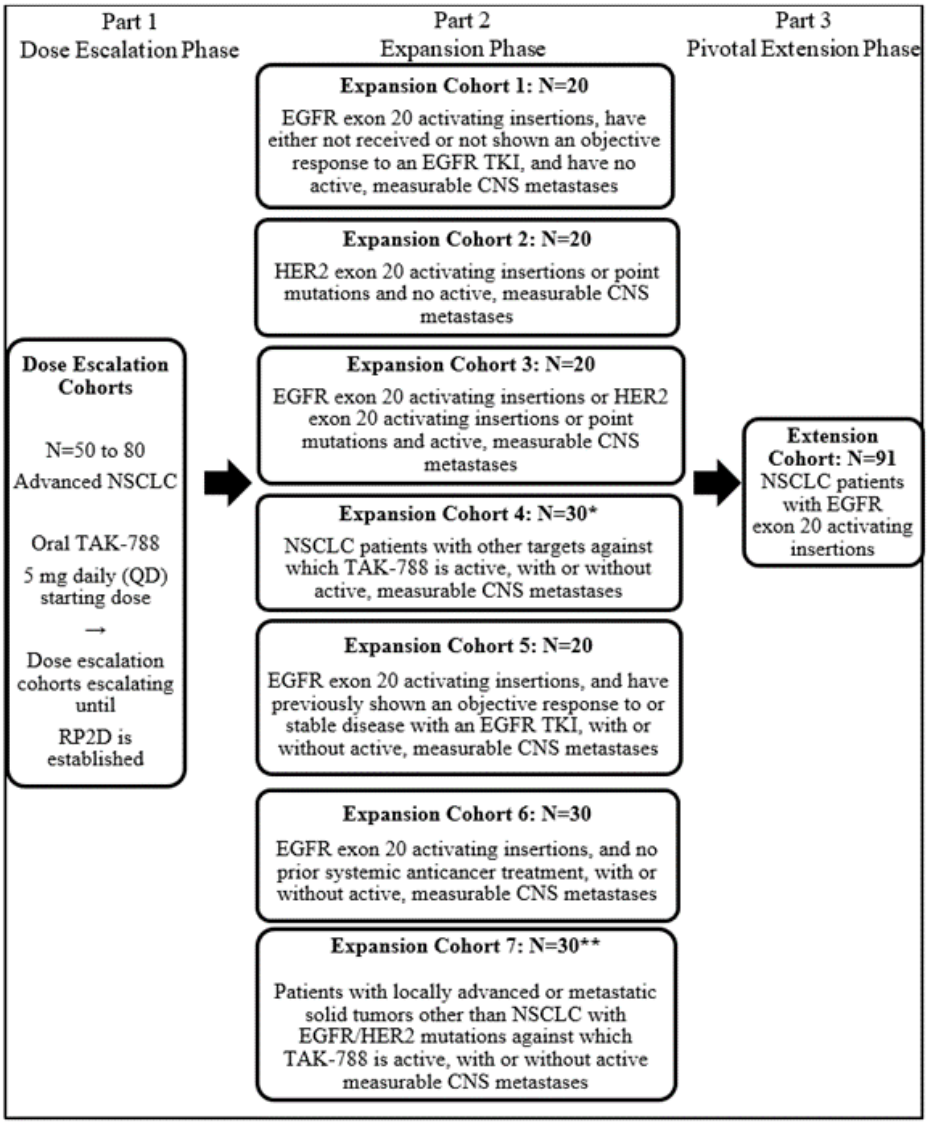
3.3.4.2. Main study

AP32788-15-101
A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumour Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer
(EudraCT Number: 2016-001271-68) (ClinicalTrials.gov Id: NCT02716116)

Study AP32788-15-101 is an uncontrolled, open-label phase 1/2 first-in-human study with a dose escalation phase (part 1) and a consecutive dose expansion phase (part 2) in initially 4 currently 7 different molecularly and histologically defined cohorts. Enrolment began in June 2016, dose expansion cohorts opened in January 2018. Based on data from the dose escalation and dose expansion phase in October 2018 the applicant amended the study and added an extension phase (part 3) to the study, including patients with previously treated locally advanced or metastatic NSCLC whose tumours harbour EGFR exon 20 insertion mutations. As to protocol amendment 4 from October 2018, part 3 of the study was added with the aim to provide pivotal evidence in an MAA for the included population and was to be analysed when all patients had had the opportunity to be followed for 6 cycles, which resulted in a data cut-off date of 29 May 2020. However, , the FDA advised to include a pooled prior

platinum analysis set as an additional analysis set and the statistical analysis plan was revised accordingly in August 2020. As to the applicant the decision to analyse the pooled prior platinum patients across Part 1, Part 2 and Part 3 in Study 101 at the recommended dose 160 mg was made prior to obtaining efficacy data from Part 3 (the originally designed pivotal extension cohort to support registration). This decision was made to take into consideration of analysing a more homogeneous population as defined by prior platinum chemotherapy treatment. To provide additional follow-up of the response data, and add to the characterisation of mobocertinib's treatment effect, another data cut-off was planned to give the majority of responding patients an opportunity to be followed for at least 6 months from the onset of response.

Figure eff 1 schematic study design of study AP32788-15-101



Source: AP32788-15-101 study protocol, amendment 6 (page 43)

Methods

Study Participants

Key inclusion criteria

General inclusion criteria (all parts and all cohorts)

All patients must meet all of the following general inclusion criteria for study entry.

1. Have histologically or cytologically confirmed locally advanced (and not a candidate for definitive therapy) or metastatic disease (Stage IIIB or IV). For all cohorts except Expansion Cohort 7, the locally advanced or metastatic disease is NSCLC. For Expansion Cohort 7, the locally advanced or metastatic disease is any solid tumour other than NSCLC.
2. Must have sufficient tumour tissue available for analysis (see Laboratory Manual for specific requirements). For patients in the expansion cohorts and in the extension cohort, tumour tissue obtained after progression on the most recent prior therapy is preferred.
3. Must have measurable disease by RECIST v1.1.
4. Male or female adult patients (aged 18 years or older, or as defined per local regulations).
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.

…

Cohort-specific key inclusion criteria

In addition to the general inclusion criteria above, patients must also meet all criteria for the cohort in which their entry is proposed.

Part 1: Dose escalation cohorts

1. Refractory to standard available therapies.

Part 2: Expansion cohorts

Expansion Cohort 1: NSCLC patients with EGFR exon 20 activating insertions, who have either not received or not shown an objective response to an EGFR TKI, and who have no active, measurable CNS metastases

1. Have a documented EGFR in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations.
2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.
3. Prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.
4. Not eligible for Expansion Cohort 3 (i.e. patients have active, measurable CNS metastases).

Expansion cohort 2-7: …

Part 3: extension cohort

1. Have a documented EGFR in-frame exon 20 insertion (including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation) assessed by a Clinical Laboratory Improvements Amendment (CLIA)-certified (United States [US] sites) or an accredited (outside of the US) local laboratory and sufficient tumour tissue available for central analysis (see Laboratory Manual). The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations. Note: central confirmation is not required for enrollment.
2. Must have received at least 1 prior line of therapy for locally advanced or metastatic disease and no more than 2 regimens of systemic anticancer chemotherapies for locally advanced or metastatic disease.

Treatments

The phase 2 expansion and extension cohorts received mobocertinib (TAK-788) monotherapy at the RP2D of 160 mg QD orally. Each 28-day dosing period was referred to as 1 cycle. Patients were treated with mobocertinib until they experienced PD that required an alternate therapy in the opinion of the investigator, or intolerable toxicity. Treatment could be continued after progressive disease if, in the opinion of the investigator, the patient continued to experience clinical benefit. Mobocertinib was self-

administered by the patient. Patients were to take the prescribed dose with water with or without a low-fat meal (i.e. ≤350 calories and ≤15% of calories from fat). Patients who forgot to take their scheduled dose of study drug were instructed not to make up the missed dose (if >6 hours after scheduled time of administration). Missed doses were to be recorded in an appropriate source record.

Objectives

Parts 1 and 2: Dose Escalation and Expansion Cohorts

1. To determine the safety profile of orally administered TAK-788
2. To identify the RP2D, dose-limiting toxicities (DLTs), and the MTD of TAK-788
3. To determine the PK profile of TAK-788 and its active metabolites, AP32960 and AP32914
4. To evaluate the anti-tumour activity of TAK-788 in NSCLC with EGFR or HER2 mutations
5. To explore relationships between tumour and/or plasma biomarkers and TAK-788 efficacy, safety, and/or CYP3A induction
6. To evaluate the anti-tumour activity of TAK-788 in patients with solid tumours other than NSCLC with EGFR or HER2 mutations

Part 3: Extension Cohort

Primary:

To determine the efficacy of TAK-788, as evidenced by confirmed ORR, as assessed by the IRC, in patients with locally advanced or metastatic NSCLC harbouring EGFR in-frame exon 20 insertion mutations and who have received at least 1 prior line of therapy for locally advanced or metastatic NSCLC

Secondary:

1. To further characterize the efficacy of TAK-788 as shown by confirmed ORR, as assessed by the investigator, duration of response, progression free survival (PFS), DCR, time to response, and overall survival (OS)
2. To assess the safety and tolerability of TAK-788
3. To collect sparse plasma concentration-time data of TAK-788 and its active metabolites, AP32960 and AP32914, to contribute to population PK and exposure-response analyses
4. To assess patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module, QLQ-LC13

Outcomes/endpoints

Primary Endpoints

Part 1: Dose Escalation Cohorts

The primary endpoint of the dose escalation component of the study was the RP2D of orally administered TAK-788.

Part 2: Expansion Cohorts

The primary endpoint of the expansion cohorts is the investigator-assessed confirmed ORR (using RECIST v1.1)

Part 3: Extension Cohort

The primary endpoint of the extension cohort was confirmed ORR, as assessed by the IRC, per RECIST v1.1.

Secondary Endpoints

Part 1: Dose Escalation Cohorts

1. DLTs and MTD of orally administered TAK-788

2. Safety profile of orally administered TAK-788
3. Plasma PK parameters of TAK-788 and its active metabolites (including, but not limited to, AP32960 and AP32914) after a single oral dose and at steady state after multiple oral doses

Part 2: Expansion Cohorts

1. Safety profile of orally administered TAK-788
2. Plasma PK parameters of TAK-788 and its active metabolites (including, but not limited to, AP32960 and AP32914) after a single oral dose and at steady state after multiple oral doses
3. Efficacy assessments including: confirmed ORR as assessed by an IRC, per RECIST v1.1 (except Expansion Cohort 6); best overall response, best target lesion response, duration of response, DCR, time to response, and PFS, as assessed by the investigator and IRC; and OS

Part 3: Extension Cohorts

1. Confirmed ORR, as assessed by the investigator, per RECIST v1.1
2. Duration of response, as assessed by the IRC and the investigator
3. Time to response, as assessed by the IRC and the investigator
4. DCR (the percentage of patients with best response of CR, PR, or SD), as assessed by the IRC and the investigator, per RECIST v1.1
5. PFS, as assessed by the IRC and the investigator
6. OS
7. Patient-reported symptoms (particular core symptoms of lung cancer), functioning, and HRQoL with the EORTC QLQ-C30 and QLQ-LC13

Sample size

For Dose Escalation and Expansion Cohorts, the sample size was determined based on clinical rather than statistical considerations.

For the Extension Cohort (Part 3), the sample size was determined so that it would allow the sponsor to state that the true ORR was greater than threshold response rate of 20%. 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 with a 1-sided alpha of 0.025.

Randomisation and blinding (masking)

N/A in a single-arm trial.

Statistical methods

The trial was conducted in three parts: a dose escalation phase, followed by an expansion phase and a pivotal extension phase. The efficacy analysis of the Part 3 full analysis set and the efficacy analysis of the pooled prior platinum analysis set from Study 101 form the primary basis of this submission.

Full analysis set: All patients who received at least 1 dose of mobocertinib were included in the full analysis set. Primary analyses of efficacy and safety were based on the full analysis set.

Part 3 FAS: All patients who receive at least one dose of TAK-788 and are enrolled in the Extension Cohort were included in the Part 3 FAS. The primary efficacy analysis in the pivotal extension cohort was performed using the Part 3 FAS. Secondary analyses of safety and efficacy were performed using the Part 3 FAS.

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. This analysis set served as the primary efficacy analysis population.

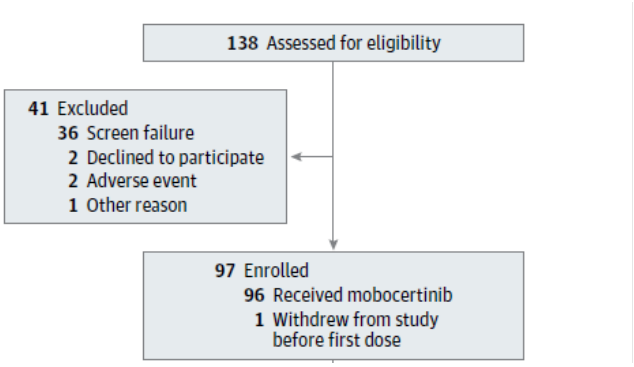
The primary endpoint of cORR, as assessed by the IRC, was tested using exact methods in the full analysis set and the pooled prior platinum analysis set. Exact two-sided 95% CIs were calculated based on the binomial distribution. The nominal p-value was calculated with an uninteresting rate of 20%.

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

Results

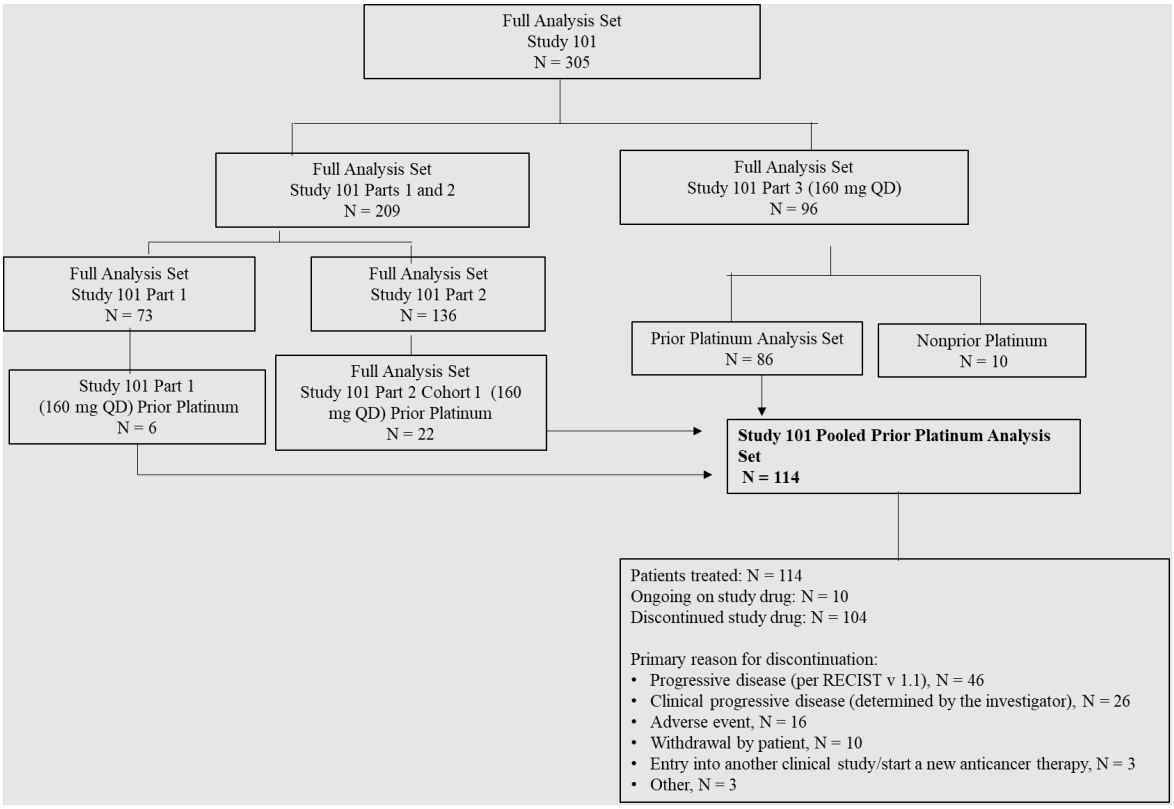
Participant flow

Figure eff 2 CONSORT Diagram of patient enrolment (extension cohort; part 3)



Source: (Zhou et al. 2021). CONSORT: Consolidated Standards Of Reporting Trials.

Figure eff 3 CONSORT Diagram of patient enrolment ('pooled prior platinum analysis set')



Source: Table 15.1.11.b, Table 15.1.3D. CONSORT: Consolidated Standards Of Reporting Trials.

Table eff 4 Disposition of patients (cut-off date 01 Nov 2020)

	Extension Cohort (Part 3, Full Analysis Set) Mobocertinib 160 mg QD (N=96)	**'pooled prior platinum analysis set' (subpopulation part 1 + 2 + 3) Mobocertinib 160 mg QD (N = 114)**
Treated n (%)	**96 (100)**	**114 (100)**
Ongoing on treatment n (%)	**25 (26.0)**	**26 (23)**
Ongoing on study n (%)	**51 (53.1)**	**55 (48)**
Reason for discontinuing study drug n (%)		
Progressive disease (RECIST)	37 (52.1)	32 (36)
Clinical progressive disease	13 (18.3)	28 (32)
Adverse event	9 (12.7)	14 (16)
Discontinued study n (%)		
Death	31 (68.9)	45 (76)

Withdrawal by patient	11 (24.4)	10 (17)
Time on study (months)		
Mean (SD)	11.0 (4.30)	13.37 (7.418)
Median (min, max)	12.5 (1, 19)	13.01 (1.2, 36.1)

Source: 'summary of clinical efficacy' table 2a and 2e; cut-off date 01 Nov 2020

Study sites

Between June 2016 and February 2020, a total of 260 patients were enrolled at 26 study centres in the US in Parts 1 and 2.

Between February 2019 and November 2019, a total of 97 patients were enrolled at 38 study centres in 9 countries in Part 3. By region, 57 patients were enrolled from 17 sites in Asia, 30 patients were enrolled from 15 sites in North America, and 10 patients were enrolled from 7 sites in Europe. Of the 38 sites that enrolled patients in part 3, 8 sites included ≥50% of the part 3 full analysis set' (49/96). Study site 9001 was by far the largest study site enrolling 15 patients into part 3, the second largest site included 6 patients.

Of note, the sites that enrolled patients for part 1 and part 2 of the study did not enrol patients in part 3 and vice versa, i.e. part 3 of study AP32788-15-101 was performed in different study sites than part 1 and 2 of study AP32788-15-101.

Recruitment

First patient treated (part 1, dose escalation):	June 2016
First patient treated (part 2, dose expansion):	January 2018
First patient treated (part 3, extension cohort):	February 2019
Last patient included (part 3, extension cohort):	November 2019
First data cut-off:	29 May 2020 (study ongoing)
Second data cut-off:	01 Nov 2020 (study ongoing)
Third data cut-off:	01 Nov 2021 (study ongoing)
Release date of CSR:	15 January 2021 and 03 May 2021 respectively

Conduct of the study

Changes in the conduct of the study or planned analysis (protocol amendments)

Table eff 5 Protocol Amendment History

Protocol Version (Global)	Amendment Date	Primary Rationale for Amendment
Original protocol	21 November 2015	Not applicable
Amendment 1	22 March 2017	To amend description of the drug product formulation to allow for multiple strengths of capsules and tablets to be used and to amend the number of dose levels and patients enrolled in Part 1 of the study to establish the RP2D.
Amendment 2	02 March 2018	To update the inclusion criterion cutoff for creatinine clearance.
Amendment 3	03 July 2018	To update the protocol to add 3 additional expansion cohorts and to modify the inclusion criteria and sample size for expansion cohort 4.
Amendment 4	11 October 2018	To update the protocol to add Part 3 of the study (a phase 2 pivotal extension cohort). Guidance was also added for the use of CYP3A substrates (including hormonal contraceptives)

Table eff 5 Protocol Amendment History

Protocol Version (Global)	Amendment Date	Primary Rationale for Amendment
		following emerging PK data that suggested autoinduction (likely via induction of CYP3A) following multiple-dose administration of mobocertinib at 160 mg QD.
Amendment 5	13 August 2019	To revise the primary endpoint for expansion cohort 6 from investigator-assessed objective response rate to IRC-assessed confirmed objective response.
Amendment 6	02 September 2020	To update the per-protocol definition and incorporate changes due to coronavirus disease 2019.
Amendment 7	08 December 2021	To add management and dose modification guidelines for decreased ejection fraction, cardiac failure, and QTc prolongation; diarrhea; amylase/lipase elevation; and additional TEAEs deemed TAK-788 related and not otherwise noted, to update list of drugs known to be associated with the development of Torsades de pointes, and to update sponsor's legal entity name and address.

Source: AP32788-15-101 Protocol Amendment 7 08 December 2021 (Protocol Amendment 7 Summary and Rationale and Appendix F Protocol History).

CYP: cytochrome 450; IRC: independent review committee; PK: pharmacokinetic; QD: once daily; QTc: heart-rate corrected QT interval; RP2D: recommended phase 2 dose; TEAE: treatment-emergent adverse event.

Protocol compliance

The presented protocol violations are not considered having a relevant impact on the efficacy outcome of the study.

GCP-inspection findings

One GCP site inspection has been performed by the FDA at the University of California San Diego (Moores Cancer Center, La Jolla, California, USA) in May 2021. Nine subjects from the inspected site were included into study 101 part 2, two of these 9 subjects are part of the post-hoc defined 'pooled prior platinum analysis set'. No significant observations are reported (no FDA Form 483 was issued).

Baseline data

Table eff 6 Key Demographics (Data Cutoff 01 November 2020)

	Extension Cohort (Part 3, Full Analysis Set) Mobocertinib 160 mg QD (N=96)	'pooled prior platinum analysis set' (subpopulation part 1 + 2 + 3) Mobocertinib 160 mg QD (N = 114)
Age (years)		
Mean (SD)	59.1 (11.69)	59.6 (11.53)
Median (Min, Max)	59.0 (27, 80)	60.0 (27.84)
Age categories, n (%)		
18 – 49 years	20 (20.8)	?
50 – 64 years	41 (42.7)	?

65 – 74 years	27 (28.1)	?
75 – 84 years	8 (8.3)	?
≥85 years	0	?
Gender, n (%)		
Male	34 (35.4)	39 (34.2)
Female	62 (64.6)	75 (65.8)
Race, n (%)		
Asian	66 (68.8)	68 (59.6)
Asian Indian	2 (2.1)	0
Chinese	42 (43.8)	0
Japanese	6 (6.3)	0
Korean	13 (13.5)	0
Not reported	3 (3.1)	1 (0.9)
Black or African American	2 (2.1)	3 (2.6)
White	28 (29.2)	42 (36.8)
Geographic region, n (%)		
Asia Pacific (China, Japan, other)	57 (59.4)	55 (48.2)
Europe	10 (10.4)	6 (5.3)
North America	29 (30.2)	53 (46.5)

Source: CSR cut-off date 29 May 2020 table 47; Table 15.1.7.D

Table eff 7 Key disease characteristics at baseline (Data Cutoff 01 November 2020)

	Extension Cohort (Part 3, Full Analysis Set) Mobocertinib 160 mg QD (N=96)	**'pooled prior platinum analysis set' (subpopulation part 1 + 2 + 3) Mobocertinib 160 mg QD (N = 114)**
Time since initial diagnosis (months)		
Mean (SD)	21.30 (25.255)	23.80 (27.915)
Median (Min, max)	11.93 (1.1, 137.3)	14.72 (1.1, 161.8)
Stage at study entry, n (%)		
IIIA	0	0

IIIB	2 (2.1)	1 (0.9)
IV	94 (97.9)	113 (99.1)
Histopathological classification of NSCLC at study entry, n (%)		
Adenocarcinoma	95 (99.0)	112 (98.2)
Squamous	1 (1.0)	1 (0.9)
Large cell	0	1 (0.9)
Site involvement at study entry, n (%)		
Brain	33 (34.4)	40 (35.1)
Bone	39 (40.6)	?
Liver	17 (17.7)	?
Lung	90 (93.8)	?
Other	79 (82.3)	?
Smoking status as of informed consent, n (%)		
Never	70 (72.9)	81 (71.1)
Current	2 (2.1)	2 (1.8)
Former	24 (25.0)	31 (27.2)
ECOG performance status, n (%)		
0	28 (29.2)	29 (25.4)
1	68 (70.8)	85 (74.6)

Source: CSR cut-off date 29 May 2020 table 48; Table 15.1.8D

Table eff 8 Mutation Status - Extension Cohort (Part 3, Full Analysis Set)

	Local Laboratories (N=96)	**Central Laboratories (N = 50)**
EGFR method of assessment		
Sequencing	37 (38.5)	20 (40.0)
PCR	28 (29.2)	13 (26.0)
Other	31 (32.3)	17 (34.0)
EGFR exon 20 insertion mutation	96 (100)	50 (100)
Type of sample		
Tumour DNA	78 (81.3)	43 (86.0)
Plasma Cell Free DNA	8 (8.3)	5 (10.0)

Other	10 (10.4)	2 (4.0)
EGFR exon 20 insertion mutation list		
A767_V769insASV	16 (16.7)	12 (24.0)
S768_D770insSVD	10 (10.4)	4 (8.0)
N771_H773insNPH	5 (5.2)	4 (8.0)
Other	51 (53.1)	22 (44.0)
Specific insertion unknown	14 (14.6)	8 (16.0)
Other EGFR mutations		
Common (DEL19/L858R)	2 (2.1)	2 (4.0)
Amplification	3 (3.1)	1 (2.0)
Other	4 (4.2)	3 (6.0)
Other genetic mutations	29 (30.2)	13 (26.0)

Source: CSR cut-off date 29 May 2020 table 49 + 50

Table eff 9 Mutation Status - local Laboratories (Data Cutoff 01 November 2020)

	Extension Cohort (Part 3, Full Analysis Set) Mobocertinib 160 mg QD (N=96)	**'pooled prior platinum analysis set' (subpopulation part 1 + 2 + 3) Mobocertinib 160 mg QD (N = 114)**
EGFR method of assessment		
Sequencing[a]	37 (38.5)	55 (48.2)
PCR	28 (29.2)	25 (21.9)
Other	31 (32.3)	32 (28.1)
EGFR exon 20 insertion mutation	96 (100)	114 (100.0)
Type of sample		
Tumour DNA	78 (81.3)	71 (62.3)
Plasma Cell Free DNA	8 (8.3)	6 (5.3)
Other	10 (10.4)	9 (7.9)
Missing[c]	28 (29.2)	28 (24.6)
EGFR exon 20 insertion mutation list[b]		
A767_V769insASV	16 (16.7)	20 (17.5)

S768_D770insSVD	10 (10.4)	10 (8.8)
N771_H773insNPH	5 (5.2)	8 (7.0)
Other	51 (53.1)	48 (42.1)
Specific insertion unknown	14 (14.6)	29 (25.4)
Other EGFR mutations		
Common (DEL19/L858R)	2 (2.1)	1 (0.9)
C797x (resistant)	0	0
Uncommon (other substitution)	0	1 (0.9)
Amplification	3 (3.1)	4 (3.5)
Other	4 (4.2)	3 (2.6)
Other genetic mutations		
Yes	29 (30.2)	26 (22.8)
No	?	0
Missing	?	88 (77.2)

Source: CSR cut-off date 29 May 2020 table 49; Table 15.1.9D

[a] Sequencing included Sanger sequencing and next-generation sequencing.
[b] Patients may have more than 1 mutation.
[c] Type of sample was not collected for the 28 patients from Parts 1 and 2 of Study 101.

Table eff 10 Prior anticancer therapies by type (Data Cutoff 01 November 2020)

	Extension Cohort (Part 3, Full Analysis Set) Mobocertinib 160 mg QD (N=96)	**'pooled prior platinum analysis set' (subpopulation part 1 + 2 + 3) Mobocertinib 160 mg QD (N = 114)**
The most common prior anticancer lines		
Pemetrexed	80 (83.3)	101 (89)
Carboplatin	59 (61.5)	83 (73)
Cisplatin	29 (30.2)	36 (32)
Pembrolizumab	23 (24.0)	26 (23)
Bevacizumab	21 (21.9)	32 (28)
Afatinib	12 (12.5)	15 (13)
Gemcitabine	9 (9.4)	12 (11)
Docetaxel	7 (7.3)	11 (10)

Nivolumab	6 (6.3)	19 (17)
Osimertinib	6 (6.3)	0
Paclitaxel	0	10 (9)
Number of prior systemic anticancer lines		
0	0	0
1	49 (51.0)	47 (41)
2	30 (31.3)	36 (32)
3 or more	17 (17.7)	31 (27)
Number of prior systemic anticancer lines		
Mean (SD)	1.7 (0.88)	?
Median (min, max)	1.0 (1, 4)	2.0 (1, 7)
Patients with prior chemotherapy	90 (93.8)	114 (100)
platinum-based CTx	86 (89.6)	114 (100)
platinum-based CTx as most recent line of therapy	?	66 (58)
Patients with prior TKI	30 (31.3)	?
Patients with prior EGFR TKI	?	29 (25)
Patients with prior immunotherapy	33 (34.4)	49 (43)
Patients with prior radiotherapy in the brain	24 (25.0)	24 (21)

Source: CSR cut-off date 29 May 2020 table 51; Table 15.1.15D

Numbers analysed

Full analysis set (FAS):

All patients who received at least 1 dose of mobocertinib were included in the full analysis set. Primary analyses of efficacy and safety were based on the full analysis set.

Part 3 FAS:

All patients who receive at least one dose of TAK-788 and are enrolled in the Extension Cohort were included in the Part 3 FAS. The primary efficacy analysis in the pivotal extension cohort was performed using the Part 3 FAS. Secondary analyses of safety and efficacy were performed using the Part 3 FAS.

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. This analysis set served as the primary efficacy analysis population for the applicant.

Per-protocol population:

Previously treated patients dosed at 160 mg with EGFR exon 20 insertion mutations who had measurable disease at baseline per the IRC and had at least 2 postbaseline disease assessments unless the reason for having fewer than 2 disease assessments was patient death or study drug discontinuation due to toxicity or documented PD.

Table eff 11 numbers analysed

	n
Full analysis set (FAS) (full population part 1 + 2 + 3)	357 (part 1 + 2: 260; part 3: 97)
Part 3 Full Analysis Set (extension cohort)	97
'pooled prior platinum analysis set' (subpopulation from parts 1 + 2 + 3)	114
Per protocol population (PP) (predefined only for extension cohort; part 3)	86 (88.7)

Outcomes and estimation

Table eff 12 Study AP32788-15-101 efficacy endpoints (cut-off date 01 Nov 2020 and 01 Nov 2021)

	Extension Cohort (Part 3, Full Analysis Set) Mobocertinib 160 mg QD (N=96)		**'pooled prior platinum analysis set' (subpopulation part 1 + 2 + 3) Mobocertinib 160 mg QD (N = 114)**	
Cut-off date	**01 Nov 2020**	**01 Nov 2021**	**01 Nov 2020**	**01 Nov 2021**
cORR (IRC) n (%) [95% CI] CR	24 (25.0) [16.7, 34.9] 0	25 (26.0) [17.6, 36.0] 1	32 (28.1) [20.06, 37.26] 0	32 (28.1) [20.06, 37.26] 1
DoR (IRC) (KM estimate) median (months) [95% CI]	- [5.55, -]	?	17.48 [7.39, 20.30]	15.77 [7.39, 19.35]
cORR (INV), n (%) [95% CI]	31 (32.3) (23.1, 42.6)	31 (32.3) [23.1, 42.6]	40 (35.1) [26.38, 44.59]	40 (35.1) [26.38, 44.59]
DoR (INV) (KM estimate) median (months) [95% CI]	?	?	11.17 [5.55, NE]	13.90 (5.55, 19.35)
PFS (IRC) (KM estimate) median (months) [95% CI] events n (%)	7.33 [5.52, 9.13]	?	7.29 [5.52, 9.23]	7.29 [5.52, 9.23] 76/114 (67)
OS (KM estimate) median (months)	-	?	23.95	20.17

[95% CI] events n (%)	[13.14, -]		[14.55, 28.81]	[14.88, 25.26] 66/114 (58)
Follow-up time median (months) [95% CI]	?	?	14.16 [13.17, 14.62]	25.79 [24.57, 26.74]
cORR: confirmed objective response rate; CR: complete remission; DoR: duration of response; IRC: by independent review committee; OS: overall survival; PFS: progression-free survival				

Source 'summary of clinical efficacy' table 2b and 2f and CSR cut-off date 01 Nov 2020; 'Responses clinical TLFs part 1' tables 15.2.2.b, 15.2.2.D, 15.2.10D, 15.2.11D, 15.2.13D, 15.2.14.D' cut-off date Nov 2021

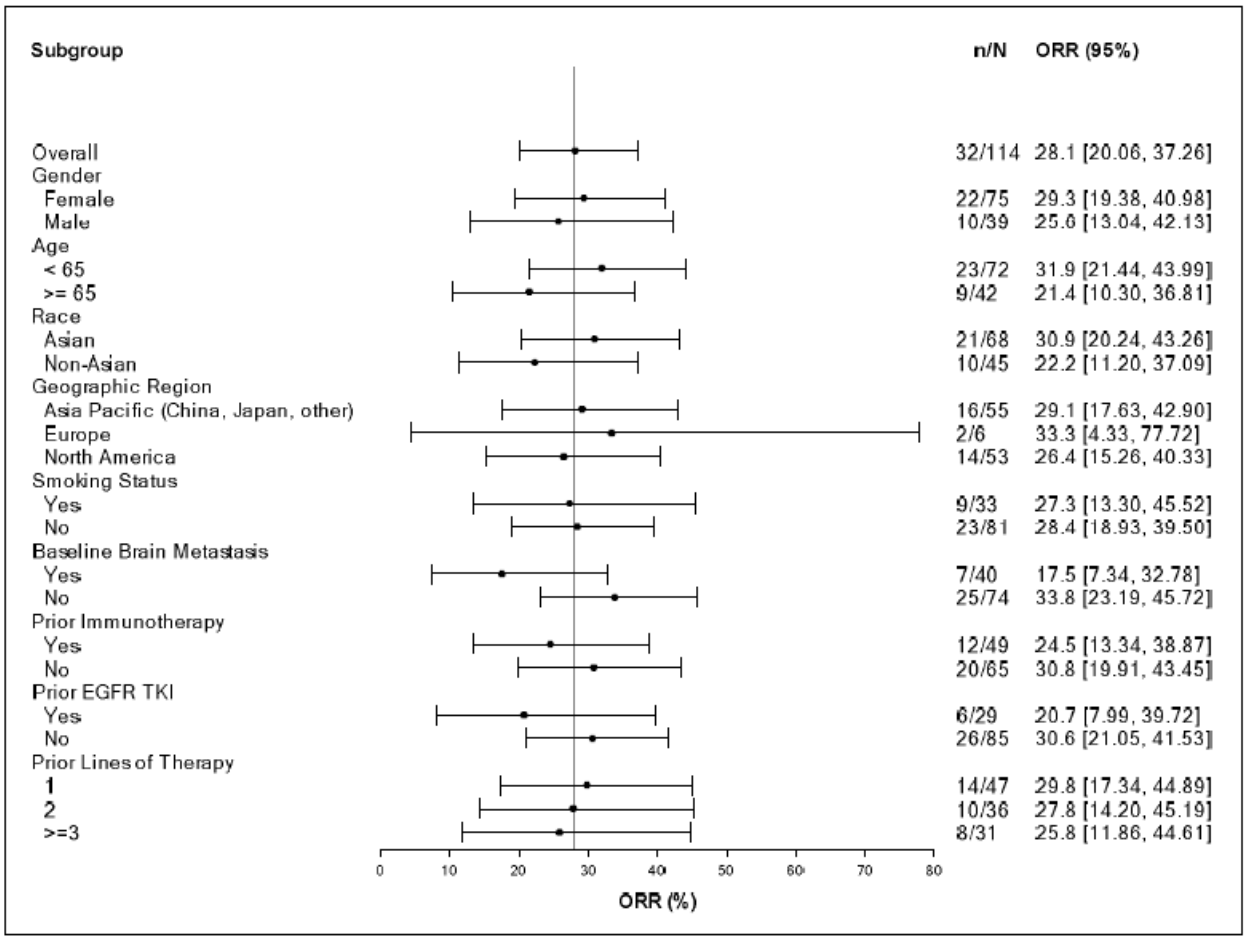
Anticancer therapy after disease progression

As of the 01 November 2020 data cut-off, 65 patients in the pooled prior platinum analysis set had disease progression by IRC; these progressions were analysed as PFS events per RECIST criteria. Of these, 40 patients (61.5%) stayed on mobocertinib for at least 1 month. Of those who continued to receive mobocertinib, the median time continued post progression was 1.89 months (range, 0.0 to 14.9 months). 15.4% of those who progressed continued to stay on mobocertinib for ≥6 months, with approximately 5% staying on it for ≥12 months.

A total of 37.7% of patients in the pooled prior platinum analysis set discontinued study treatment and received a subsequent systemic anticancer therapy. The subsequent anticancer therapies included chemotherapy (24.6%), EGFR TKIs (11.4%), and immunotherapy (7.9%). Of those who got subsequent therapy, 20.2% received 3+ subsequent systemic anticancer regimens as of the 01 November 2020 data cut-off.

Ancillary analyses

Figure eff 3 Forest plot of IRC-assessed ORR (cut-off 01 Nov 2020) ('pooled prior platinum analysis set')



Source CSR cut-off date 01 Nov 2020, figure 3.d

Table eff 13 Subgroup Analysis of IRC-Assessed cORR (Pooled Prior Platinum Analysis Set)

	Number (%) of Patients [95% CI] [a]
	IRC-Assessed cORR [b] Mobocertinib 160 mg QD (N = 114)
***EGFR* exon 20 insertion distribution [a]**	
Common insertion	15 (31.9) [19.09, 47.12] (n = 47)
769_ASV	8 (32.0) [14.95, 53.50] (n = 25)
770_SVD	2 (15.4) [1.92, 45.45] (n = 13)
773_NPH	5 (55.6) [21.20, 86.30] (n = 9)
Uncomon insertion	12 (25.0) [13.64, 39.60] (n = 48)
Not established	5 (31.3) [11.02, 58.66] (n = 16)
Insertion structure	
Near loop	20 (28.6) [18.40, 40.62] (n = 70)
Far loop	6 (25.0) [9.77, 46.71] (n = 24)

Source: Study 101 Pooled Analysis Listing 15.2.2.8D (data cutoff: 01 November 2020).
cORR: confirmed objective response rate; CR: complete response; EGFR: epidermal growth factor receptor; IRC: independent review committee; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; QD: once daily.
[a].Two-sided 95% exact CI, computed using Clopper-Pearson method.
[b] IRC-assessed cORR is the primary endpoint for extension cohort. IRC-assessed cORR is defined as the proportion of patients who are confirmed to have achieved CR or PR, per RECIST v1.1, after the initiation of study treatment as assessed by the IRC.

3.3.4.3. Summary of main efficacy results

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

Table eff 13 Summary of Efficacy for Study AP32788-15-101

Title: A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumour Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer			
Study identifier	AP32788-15-101 **EudraCT Number:** 2016-001271-68 **NCT Number:** NCT02716116 **Universal Trial Number:** U1111-1217-7205		
Design	This is an open-label, single-arm, Phase 1/2 first-in-human study with a dose-escalation phase (Part 1), a consecutive expansion phase in 7 distinct disease cohorts (Part 2) and an extension cohort in patients with previously treated NSCLC whose tumour harboured *EGFR* exon 20 insertion mutation (Part 3). Part 3 was the pre-specified pivotal part.		
	Duration of main phase:		first patient treated June 2016 (study ongoing)
Hypothesis	Exploratory; no pre-planned efficacy hypothesis		
Treatments groups	'Part 3 Full analysis set' (extension cohort) (pre-specified primary analysis set)		160 mg QD orally, continuously in 28-day cycles (N = 96)
	'Pooled prior platinum' (post-hoc defined analysis set)		160 mg QD orally, continuously in 28-day cycles (N = 114)
Endpoints and definitions	Primary endpoints	cORR (IRC)	Confirmed objective response rate, as assessed by the IRC, per RECIST v1.1.
	Secondary endpoint	DoR (IRC)	Duration of response, as assessed by the IRC and the investigator.
	Secondary endpoint	PFS (IRC)	Progression-free survival, as assessed by the IRC and the investigator.
	Secondary endpoint	OS	Overall survival
Database lock	01 November 2021 (data cut-off date)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	'Part 3 Full Analysis Set' (extension cohort) *(pre-specified primary analysis set)* All patients who received at least one dose of mobocertinib and were enrolled in the Extension Cohort were included in the Part 3 FAS.		

	'Pooled prior platinum analysis set' *(post-hoc defined subpopulation of part 1, 2 and 3)* It pooled patients with metastatic NSCLC with EGFR exon 20 insertion mutations who had previously been treated with platinum-based chemotherapy and who received mobocertinib at 160 mg QD from Part 1 [n = 6], Expansion Cohort 1 of Part 2 [n = 22], and Part 3 [n = 86].		
Descriptive statistics and estimate variability	Treatment group	'Part 3 Full Analysis Set' (pre-specified primary analysis set)	'Pooled Prior Platinum Analysis Set' (post-hoc defined subpopulation)
	Number of subjects	96	114
	cORR (IRC) , n (%) [95% CIs]	25 (26.0) [17.6, 36.0]	32 (28.1) [20.06, 37.26]
	DoR (IRC), (KM estimate), median (months) [95% CIs]	?	17.48 [7.39, 20.30]
	PFS (IRC), (KM estimate) median (months) [95% CIs]	?	7.29 [5.52, 9.23]
	OS, (KM estimate) median (months) [95% CIs]	?	20.17 [14.88, 25.26]
Notes	cORR (IRC) results are based on partial responses (PR), only one complete response (CR) was reached in the pivotal study.		
cORR: confirmed objective response rate; DoR: duration of response; IRC: independent review committee; NE: not evaluable (immature); NSCLC: non–small cell lung cancer; OS: overall survival; PFS: progression-free survival; QD: once daily			

3.3.4.4. Clinical studies in special populations

Table eff 12 Experience in elderly subjects

	Age 65-74 n (%)	**Age 75-84 n (%)**	**Age 85+ n (%)**
Controlled Trials	0	0	0
Non Controlled trials	83 (29)	29 (10)	2 (0.7)

3.3.4.5. In vitro biomarker test for patient selection for efficacy (OC)

Scientific rationale for the choice of the predictive in vitro biomarker test (e.g. prevalence, relation to disease mechanism).

Mobocertinib is a potent and selective inhibitor of EGFR exon 20 insertions that demonstrated inhibitory activity against EGFR with this mutation (see clinical and non-clinical pharmacodynamics). Therefore, the scientific rationale to have – next to histology – a positive EGFR exon 20 insertion mutation status as key inclusion criterion defining the target population for mobocertinib treatment is acknowledged. However, whether 'EGFR exon 20 insertion mutation status' is a predictive biomarker remains to be clarified (see below, clinical validity / cut-point selection).

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method.

One analytical method used for central analysis of the samples (ODxT Test, ThermoFisher Scientific) is briefly described. It is however unclear if this was the only centrally applied test method. In addition, information on the locally applied biomarker tests (LLT) to confirm biomarker positivity upon patient enrollment is missing.

Analytical validation strategy:

Analytical validation strategy for the ODxT test for the detection of EGFR exon 20 insertions is summarized. The values of the presented validation parameters are within acceptable limits.

No information on performance of the locally applied analytical procedures (LLT) to identify biomarker positive patients has been given. The information provided is not deemed sufficient to conclude on concordance of the locally applied analytical methods with the centrally applied confirmation assay(s). Acceptance criteria for concordance need to be defined and justified.

Clinical validation strategy:

Clinical validity (sensitivity/specificity) should be described either by correlation with a clinical endpoint (for novel assays) or –if available- by concordance study with a clinically valid reference assay

The information provided is not sufficient to show clinical validity of the biomarker tests used to define biomarker positivity (i.e. "EGFR exon 20 insertion mutation") of the patients included into the pivotal study 101.

Cut-point selection should be described and discussed in detail since it is of particular importance for the benefit /risk assessment.

No information regarding cut-point selection(s) is provided.

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

N/A

3.3.4.7. Supportive studies

Because treatment outcomes are not well established, evidence about the efficacy of the used agents in the patient population applied for is scarce and to support the pivotal single-arm clinical study data, the applicant collected and conducted two non-interventional retrospective analyses of RWD on patients with NSCLC and EGFR exon 20 insertion mutations as a historical benchmark, namely study TAK-788-5002 and 'German chart review'.

Study TAK-788-5002

This study was a non-interventional retrospective study that did not impose a treatment protocol, any diagnostic/interventional procedure, or a visit schedule. It used longitudinal data from the Flatiron Health Research Database, a US-nationwide electronic health record (EHR)-derived database, representing more than 2.4 million active US cancer patients treated at over 800 unique sites of care.

Methods

The primary objective was to describe the anti-tumour effectiveness of currently used standard of care, based on the following endpoints:

- Primary endpoint: confirmed real-world overall response rate (confirmed rwORR). Real-world response (rwR) is an abstracted variable that identifies clinician assessment of change in disease burden following radiographic imaging during a line of therapy. In the Flatiron Health database, EHR data elements are systematically analysed and extracted to obtain rwR.
- Secondary endpoints: real-world duration of response (rwDOR), real-world disease control rate (rwDCR), overall survival (OS), real-world progression-free survival (rwPFS), real-world time to treatment discontinuation (rwTTD), and real-world time to next treatment (rwTTNT).

All objectives were assessed separately in two patient populations:

- TN patients: patients who received first-line therapy for advanced NSCLC.
- Trial-aligned patients: patients who had been previously treated for advanced NSCLC 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.

Additional analyses were conducted to assess the objectives in the following two patient populations:

- Previously treated patients: patients who had been previously treated for advanced NSCLC.
- Prior platinum trial-aligned patients: trial-aligned patients (as defined above) but who had also been previously treated with platinum-based chemotherapy.

Confirmed rwORR was calculated as the number of patients with at least one PR or CR determination followed by a subsequent PR, CR, or SD determination, of any duration divided by the total number patients in that cohort. For assessment of responders, patients without an assessment of disease response were treated as non-responders.

Time to event endpoints were analysed by Kaplan-Meier methodology.

Outcomes and estimation

A total of 237 patients with advanced NSCLC with EGFR exon 20 insertion mutations were identified in the Flatiron database. 129 TN patients and 114 previously treated patients were then identified to be eligible for the study. 63 patients were included in the trial-aligned patient cohort. Among those, 50 patients received platinum-based chemotherapy prior to the index date.

Table 11.d presents a summary of confirmed rwORR (including patients without an assessment of disease response → these patients were treated as non-responders) and Table 11.e a summary of OS.

Table 11.d Confirmed Real-World Overall Response Rate, Real-World Disease Control Rate, and Real-World Duration of Response

Endpoint	Treatment-Naïve Patients (N=129)	Previously Treated Patients (N=114)	Trial-Aligned Patients (N=63)	Prior Platinum Trial-Aligned Patients (N=50)
Confirmed rwORR				
n (%)	24 (18.6%)	11 (9.6%)	7 (11.1%)	7 (14.0%)
95% CI	12.3%, 26.4%	4.9%, 16.6%	4.6%, 21.6%	5.8%, 26.7%
rwDCR				
n (%)	71 (55.0%)	47 (41.2%)	30 (47.6%)	22 (44.0%)
95% CI	46.0%, 63.8%	32.1%, 50.8%	34.9%, 60.6%	30.0%, 58.7%
KM estimate for rwDOR, months [a]				
Median	10.0	10.9	6.1	6.1
95% CI	6.2, 20.7	3.3, 23.0	3.3, 23.0	3.3, 23.0

Table 11.e Overall Survival, Real-World Progression-Free Survival, Real-World Time to Treatment Discontinuation, and Real-World Time to Next Treatment

Endpoints [a]	Treatment-Naïve Patients (N=129)	Previously Treated Patients (N=114)	Trial-Aligned Patients (N=63)	Prior Platinum Trial-Aligned Patients (N=50)
OS follow-up time, months [b]				
Median (95% CI)	24.0 (17.5, 37.1)	23.8 (14.0, 31.9)	23.8 (16.3, 31.9)	24.2 (16.3, NE)
OS, months				
Median (95% CI)	17.0 (11.2, 19.5)	13.6 (8.2, 15.4)	13.6 (8.3, 17.8)	11.5 (7.9, 16.6)
rwPFS, months				
Median (95% CI)	5.2 (3.1, 6.9)	3.7 (2.7, 5.2)	3.4 (2.5, 6.4)	3.3 (2.3, 5.9)
rwTTD, months				
Median (95% CI)	3.1 (2.3, 4.9)	2.8 (2.1, 3.6)	2.8 (2.0, 3.7)	2.8 (2.0, 3.7)
rwTTNT, months				
Median (95% CI)	6.1 (4.3, 8.4)	4.2 (3.3, 5.9)	4.4 (3.0, 7.1)	4.6 (3.0, 7.4)

Confirmed rwORR was 14.7% (95% CI 7.6,24.7) among previously treated patients with tumour assessment (N=75), 14.6% (95% CI 6.1,27.8) among trial-aligned patients with tumour assessment (N=48), 18.4% (95% CI 7.7,34.3) among prior platinum trial-aligned patients with tumour assessment (N=38).

German chart review

In addition to the RWD study using EMRs from US, the applicant collaborated with academic investigators to conduct a retrospective chart review in Germany. Longitudinal data were collected and analysed from patients with NSCLC with EGFR and HER2 exon 20 insertion mutations from 12 academic thoracic oncology centres across Germany.

Methods

Primary objective of this study was the efficacy of currently used standard of care for the first and subsequent treatment lines in cohorts 1 (EGFR+) and 2 (HER2+), measured as the overall response rate (ORR). As secondary endpoints the efficacy of currently used standard of care for the first and subsequent treatment lines in the cohorts 1 (EGFR+) and 2 (HER2+) measured as: duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), time-to-treatment-failure (TTF), overall survival (OS), confirmed ORR (cORR).

This study included adult (>18 years old) patients with histologic diagnosis of NSCLC and insertions in the exon 20 of EGFR or HER2, who received systemic treatment for stage IV disease and were evaluable for tumour response.

The ”post-platinum” subset, i.e. patients that had received platinum-based chemotherapy (alone or in combination with bevacizumab or immunotherapy) in the first line or within one year before start of the first line, as part of initial definitive treatment, was also analysed separately.

Tumour response was reported according to RECIST v1.1. To this end, radiologic images or radiologic reports were reviewed.

Outcomes and estimation

In total, data from 190 patients with Exon20 insertions (124 EGFR+, 65 HER2+) were collected from twelve thoracic oncology centres across Germany. Overall, 165 patients with advanced metastatic Exon20-insertion-positive NSCLC received systemic therapy and were evaluable for outcome (104 EGFR+ and 61 HER2+).

Table 3. cORR

cORR	1st line		2nd line		2nd-and-beyond line	
	EGFR	HER2	EGFR	HER2	EGFR	HER2
overall	13% (n=103) [2]	31% (n=60)	5% (n=57)	6% (n=33)	5% (n=106)	5% (n=58)
by treatment type						
- CHT [1]	19% (n=52)	31% (n=35)	13% (n=24)	7% (n=15)	9% (n=58)	6% (n=31)
doublet-CHT	21% (n=47)	30% (n=33)	25% (n=12)	33% (n=3)	13% (n=23)	14% (n=7)
mono-CHT	0% (n=5)	50% (n=2)	0% (n=12)	0% (n=12)	6% (n=35)	4% (n=24)
- CHT/IO	19% (n=16)	35% (n=20) [3]	0% (n=4)	0% (n=2)	0% (n=5)	0% (n=3)
- IO	0% (n=7)	20% (n=5)	0% (n=10)	9% (n=11)	0% (n=14)	7% (n=14)
- EGFR TKI	0% (n=28)	---	0% (n=19)	0% (n=5)	0% (n=29)	0% (n=10)
post-platinum:			0% (n=43)	6% (n=31)	1% (n=84)	5% (n=56)
CHT-IO			0% (n=4)	0% (n=1)	0% (n=4)	0% (n=2)
platinum-CHT			0% (n=3)	33% (n=3)	0% (n=12)	14% (n=7)
IO			0% (n=9)	9% (n=11)	0% (n=12)	7% (n=14)
EGFR TKI			0% (n=16)	0% (n=5)	0% (n=26)	0% (n=10)
mono-CHT			0% (n=11)	0% (n=11)	3% (n=30)	4% (n=23)

Table 7. Median OS of study patients in months (95% CI)

median OS	from start of 1st line		from start of 2nd line	
	EGFR	HER2	EGFR	HER2
all patients	17.8 (13.9-21.7) n=104	16.8 (10.9-22.7) n=61	9.9 (6.8-12.9) n=61	9.8 (4.4-15.3) n=35
by treatment type				
- CHT [1]	18.4 (15.2-21.5) n=53	18.1 (7.6-28.7) n=36	11.2 (8.0-14.3) n=26	6.6 (0.1-13.1) n=16
doublet-CHT	18.8 (15.9-21.6) n=47	18.5 (7.8-29.1) n=34	11.7 (0.0-25.1) n=13	20.0 (3.9-23.9) n=3
mono-CHT	8.5 (0-17.1) n=6	7.0 (3.5-10.5) n=2	9.9 (7.2-12.5) n=13	6.6 (3.1-10.1) n=13
- CHT/IO	n.r. n=16	13.8 (4.3-23.3) n=20	n.r. (n=5)	3.3 (0.4-6.1) n=2
- IO	24.7 (7.2-42.2) n=7	11.1 (5.5-16.7) n=5	4.9 (2.8-7.0) n=10	26.7 n=12
- EGFR TKI	12.6 (6.7-18.5) n=28		11.4 (4.4-18.4) n=20	5.2 (2.7-7.7) n=5
post-platinum:	18.8 (16.3-21.2) n=67	16.8 (11.9-21.7) n=54	9.9 (6.9-12.8) n=44	10.5 (3.3-17.7) n=33
CHT-IO	n.r. n=16	13.8 (4.3-23.3) n=20	n.r. n=4	n.r. n=1
platinum-CHT	18.8 (15.8-21.7) n=48	18.5 (7.8-29.1) n=34	17.7 (3.2-32.2) n=3	20.0 (3.9-23.9) n=3
IO	2.7 n=1		5.0 (3.0-6.9) n=9	26.7 n=12
EGFR TKI	19.4 n=1		11.6 (6.2-17.1) n=17	5.2 (2.7-7.7) n=5
mono-CHT	n.r. n=1		9.5 (8.6-10.4) n=11	4.1 (0.6-7.6) n=12

3.3.5. Discussion on clinical efficacy

Basics

The efficacy claims of mobocertinib monotherapy in '*adult patients with EGFR exon 20 insertion mutation-positive locally advanced or metastatic NSCLC, who have received prior platinum-based chemotherapy*' are based on a single pivotal uncontrolled phase 1/2 study, namely study AP32788-15-101.

To support this uncontrolled clinical study data, the applicant performed study TAK-788-5002, a non-interventional (observational) retrospective study using longitudinal data from the Flatiron Health Research Database, a US-nationwide electronic health record (EHR)-derived database. The aim of this analysis of real-world data (RWD) on patients with NSCLC and EGFR exon 20 insertion mutations was contextualisation of the pivotal SAT by providing a historical benchmark as supportive information. In addition to the RWD study TAK-788-5002 using EHRs from the US, the applicant collaborated with academic investigators to conduct a retrospective chart review in Germany. Longitudinal data were collected and analysed from patients with NSCLC with EGFR and HER2 exon 20 insertion mutations from 12 academic thoracic oncology centres across Germany.

To further support these results in the scope of this CMA application in the proposed 2nd-/later-line indication, the applicant proposes the ongoing randomised controlled phase 3 study TAK-788-3001, comparing mobocertinib monotherapy versus platinum-based doublet-chemotherapy in first-line treatment of patients with advanced NSCLC harbouring EGFR and HER2 exon 20 insertion mutations as key SOB.

Design and conduct of clinical studies

Pivotal study – Study AP32788-15-101

Study AP32788-15-101 is an uncontrolled, open-label phase 1/2 first-in-human study with several protocol amendments changing key elements of the study design. The study has a dose escalation phase (part 1) and a consecutive dose expansion phase (part 2) in different molecularly and histologically defined cohorts. Based on data from the dose escalation and dose expansion phase the applicant amended the study and added an extension phase (part 3) to the study, including patients with previously treated locally advanced or metastatic NSCLC whose tumours harbour EGFR exon 20 insertion mutations. This extension phase (part 3) was added with the aim to provide pivotal evidence in an MAA for the included population and was to be analysed when all patients had had the opportunity to be followed for 6 cycles, which resulted in a data cut-off date of 29 May 2020. However, the FDA advised to include a pooled prior platinum analysis set as an additional analysis set, which was based on consideration of the treatment pathway and available alternative therapy and based on the efficacy data of the 28 patients (6 from Part 1 and 22 from Part 2) whose prior treatments included platinum-based chemotherapy. Irrespectively of the question whether this analysis set was indeed added before results of Part 3 were known (which is of some doubt as the SAP introducing the analysis set was dated almost 3 months after data cut-off for Part 3), considering that the study was open-label and this analysis set includes also patients from Part 1 and Part 2 with known outcomes, it is considered as a post-hoc specified analysis set. In addition, another data cut-off was added to give the majority of responding patients an opportunity to be followed for at least 6 months from the onset of response (01 November 2020), and an additional data cut was performed in November 2021 to substantiate longer term clinical benefit of mobocertinib. Although the analysis based on the prior platinum analysis set with data cut-off 01 November 2021 provides the most mature data in the population claimed in the indication, the post-hoc specification of the analysis set and data cut-offs may lead to bias and further adds to the uncertainties.

Although part 3 of the study was added as a pivotal extension cohort, no confirmatory analysis was planned to be conducted (i.e. no pre-specified null hypothesis was tested based on part 3). However, the nominal p-value was to be calculated with an uninteresting rate of 20%. Although it is interesting to note what was seemingly considered as the threshold for significant activity by the applicant, this nominal p-value is not of relevance for drawing conclusions on efficacy as the threshold of 20% does not have clinical relevance (it is by far lower than what could be considered as 'outstanding' cORR in this context). Overall, analysis of the 'pivotal' part 3 is also considered as exploratory.

Recruitment started in June 2016 for part 1, in January 2018 for part 2 and in February 2019 for part 3. Of note, in June 2018 the applicant received CHMP scientific advice (EMEA/H/SA/3828/1/2018/III) not to perform the proposed uncontrolled extension cohort (at that point not yet started) with the aim to provide pivotal data as it was deemed "unlikely that data reported from the proposed uncontrolled extension cohort would be considered sufficient to support an approval". ORR ranges discussed in the advice were in the same range of the data presented in this current MAA.

In summary, study design, statistical methods and efficacy endpoints as defined in the study protocol could be considered appropriate for an exploratory phase 1/2 single-arm trial and in this early trial setting they sufficiently reflect the study objectives. However, the well-known limitations of a single-arm trial apply. For time to event endpoints such as OS and PFS, no isolation of drug effects is possible, as they reflect to a high degree also the tumour biology, the inherent prognosis of the disease, the patients' performance status and comorbidities (list incomplete). Therefore, efficacy assessment of the uncontrolled open-label phase 1/2 study presented as single pivotal evidence will focus on confirmed objective response rate by independent review committee assessment [cORR (IRC assessed)]. Having in mind that even for these endpoints, where drug effects can be isolated without a control group, as outcome without active treatment is predictable, direct or indirect comparisons to actively treated external controls is susceptible to selection bias and confounding such that no claims on the importance/relevance of findings compared to other therapeutic options can be made (see also below).

Supportive studies

TAK-788-5002

Study TAK-788-5002 is a non-interventional retrospective study that did not impose a treatment protocol, any diagnostic/interventional procedure, or a visit schedule. The aim of the RWD on patients with NSCLC and EGFR exon 20 insertion mutations was contextualisation of the pivotal SAT by providing a historical benchmark as supportive information. The limitations of external historical data, particularly real-world data, for providing context still need to be taken into account.

- Firstly, meaningful context can only be provided if patients from the relevant analysis sets from the pivotal SAT and RWD study are comparable with regard to baseline factors influencing prognosis. Therefore, only analyses based on study-aligned patients may provide context. However, while including only patients aligned with key eligibility criteria of pivotal study part 3 and prior platinum analysis set is a necessary requirement to achieve alignment, it is not sufficient to ensure matching of analysis populations with regard to prognostic factors. Indeed, differences were noted regarding some baseline characteristics, and additional baseline differences may be possible for additional factors where no information was available or which are yet unknown. A major difference is also that Flatiron data are US-based, while the majority of patients in the pivotal study part 3 were recruited in Asia (60%) and only 30% in North America.
- Secondly, although the attempts for standardization and providing a high data quality are acknowledged, the endpoints must still rely on the information available in EHRs such that data

quality is basically dependent on the data quality in the underlying EHR's that is not under control of the sponsor. Consequently, response or progression endpoints based on EHR where data are not collected in a systematic and standardized way cannot be considered as comparable to the corresponding endpoints based on systematic data collection within an interventional clinical trial. Even collection of mortality data from RWD is more challenging such that even analysis of OS may be susceptible to bias because of missing data.

- Generally, the relatively large proportion of patients in the analysis sets without tumour assessments (~ 25%) raises the concern that these data may not be an adequate source for a reliable evaluation of response to provide an adequate historical benchmark. It is acknowledged that excluding patients without tumour assessments from the analysis may lead to selection bias, particularly when it could be assumed that not performing tumour assessments is associated with a lower likelihood of response (e.g. if no tumour assessment is performed because of deteriorating disease). Otherwise, generally handling missing data as non-response in the analysis (i.e. assuming that all patients without tumour assessments are non-responders) probably leads to an underestimation of response, which may lead to an inappropriately low RWD benchmark, particularly considering the large proportion of patients without tumour assessments.

Due to these limitations, any claims regarding the relevance of findings from the SAT regarding response, progression or overall survival based on reference to RWD benchmark are not considered valid.

German Chart review

In addition, the applicant conducted a retrospective chart review in Germany. Longitudinal data were collected and analysed from adult patients with stage IV NSCLC with EGFR and HER2 exon 20 insertion mutations from 12 academic thoracic oncology centres across Germany. The aim of this study was the generation of RWD of cohorts of patients with advanced NSCLC and EGFR (cohort 1) or HER2 (cohort 2) exon 20 insertion mutations, respectively. Primary objective of this study was the efficacy of currently used standard of care for the first and subsequent treatment lines in cohorts 1 (EGFR+) and 2 (HER2+), measured as the overall response rate (ORR). The "post-platinum" subset, i.e. patients that had received platinum-based chemotherapy (alone or in combination with bevacizumab or immunotherapy) in the first line or within one year before start of the first line, as part of initial definitive treatment, was also analysed separately. ORR was calculated as the number of patients with PR or CR divided by the total number of evaluable patients (i.e., patients with at least one radiologic examination) within three months after treatment start in the respective cohort within the first and subsequent lines of therapy. This analysis was performed separately for the first vs. subsequent lines.

The same limitations apply as for the RWD comparison based on Flatiron database. In addition, it seems that no attempts were made to identify patients that were aligned to key eligibility criteria beside presence of mutations. It is also unclear whether measures aiming to ensure systematic assessment of RWD to provide a minimum level of data quality were in place.

Comparison of mobocertinib-treated patients to RWD

Originally, no analysis aiming for a direct comparison of mobocertinib-treated patients to external RWD controls from TAK-788-5002 and the German Chart Review was provided. Such an analysis was now provided in response to the day 120 LoQ. However, the previous assessment had already concluded that, given the limitations of such an analysis where bias cannot not be excluded, such an analysis would not provide added value to support B/R assessment. This conclusion still holds.

Efficacy data and additional analyses

Pivotal study – Study AP32788-15-101

As discussed above, all efficacy data of pivotal study AP32788-15-101 are exploratory. The strongest efficacy data provided is the prespecified primary endpoint of the extension cohort ('part 3 FAS'), being cORR (IRC) of 26% and a lower bound of the 95% confidence interval of 18%. For the post-hoc defined 'pooled prior platinum analysis set', representing the targeted indication, cORR (IRC) is higher, but still only 28% with a lower bound of the 95% confidence interval of 20%. One patient reached complete response (CR) per investigator assessment (but not per the independently reviewed cORR [IRC] data).

Furthermore, the clinical relevance of ORR (as primary efficacy endpoint) for NSCLC patients is unclear.

Having a look at investigator-assessed (INV) cORR it is noticed that response rates are constantly (at around 7%) higher compared to the independent review committee (IRC) assessment in both analysis sets. However, in order to minimise investigator bias, when a SAT with ORR as primary endpoint as pivotal evidence is provided, response assessment should be performed by a blinded independent review committee (IRC).

The study population included into extension cohort part 3 is predominantly Asian (68.8%), female (64.6%), below 65 years of age (63.5%) (median and mean age 59 years), never smokers (72.9%), 2nd-line (51%), has an ECOG status 0 or 1 (100%) and has an adenocarcinoma (99.0%) (the population of the 'pooled prior platinum analysis set' is comparable). A better survival prognosis including better response rates can be assumed for this study population in comparison to the European standard NSCLC Stage IV population. This expectation is in line with the subgroup analyses provided for the 'pooled prior platinum analysis set', showing better response rates for the above mentioned subgroups, where available.

Furthermore, it is remarkable that patient recruitment of the extension cohort (part 3) took only 10 months for 97 patients, leading to the question, why an RCT should not be feasible in the targeted population (applicable for both 'part 3 FAS' and the 'pooled prior platinum analysis set').

In conclusion, this exploratory data with a low level of evidence suggest promising clinical activity of mobocertinib monotherapy in the studied population that should be confirmed. The shown effect size of cORR is lower than what could be considered as 'outstanding' (MO).

Furthermore, the uncertainties in the efficacy estimate with a low level of evidence of the exploratory data provided make the interpretation challenging.

The median DoR, measured by IRC, was approximately 16 months in the pooled prior platinum analysis set. However, due to the low number of events and a considerable proportion of censored patients (28%), the analysis may still be considered not fully mature. Interpretation of the clinical relevance of this data is questionable due to the low number of responses reached in the pivotal study and the explorative nature of the data provided.

Due to the single-arm nature of the study, the drug effect on time-to-event outcomes such as PFS and OS cannot be isolated, and no claims can be made for these outcomes. In the setting of a CMA, the clinical benefit in terms of PFS and OS need to be confirmed by the ongoing or planned phase 3 randomized controlled trial proposed as specific obligation.

Subgroup analyses, although based on limited data, indicate lower response for patients with brain metastases at baseline. Intracranial efficacy is of clinical interest and has previously been shown for other EGFR TKIs after radiotherapy (Dodson et al, 2020). In the current study, data from a cohort

showed no objective responses in patients with measurable target lesions in the brain. This is in line with preclinical studies showing that mobocertinib does not penetrate the blood brain barrier.

Supportive studies

TAK-788-5002

Although the Flatiron database covers 2.4 million US active cancer patients, only 63 patients were included in the trial-aligned cohort and 50 patients in the prior platinum-aligned cohort. Due to these small patient numbers, precise estimates cannot be provided based on this study.

Differences between trial-aligned patients and patients from pivotal study part 3 regarding baseline demographic factors (age, race) and baseline clinical characteristics (stage, prior therapy lines) are noted.

Almost 25% of trial-aligned patients (15/63) and prior platinum-trial aligned patients (12/50) had no tumour assessments, which raises general concerns whether these data are an adequate source for a reliable evaluation of response. Patients without tumour assessment were considered as non-responders in the analysis. Obviously, this implies that in patients with tumour assessments, response rates were larger (14.6% instead of 11.1% for trial-aligned patients; 18.4% instead of 14% for prior platinum trial-aligned patients).

The 95% confidence intervals for the rwORR based on trial-aligned and prior platinum trial-aligned patients overlap with the 95% CIs for cORR based on the respective analysis populations from the pivotal SAT (for all patients as well as for patients with tumour assessments). Considering patients without tumour assessment as non-responders obviously implies that response rates were larger in patients with tumour assessments.

Due to the limitations of indirect comparisons, overlapping CIs should not be over-interpreted but add to the uncertainties that make any claims regarding the clinical meaningfulness of the outcomes from the SAT for mobocertinib based on the comparison to the RWD impossible.

German Chart review

The same limitations apply as for the RWD comparison based on Flatiron database (study TAK-788-5002). In addition, it seems that no attempts were made identify patients that were aligned to key eligibility criteria beside presence of mutations. It is also unclear whether measures aiming to ensure systematic assessment of RWD to provide a minimum level of data quality were in place. Baseline differences between EGFR+ patients from the chart review and patients from pivotal study part 3 are noted.

Due to generally limited information on alignment of these patients with patients from Part 3 of the 'pivotal' study and the prior platinum analysis set, drawing any conclusions in how far these patients provide a benchmark is difficult.

Comparison of mobocertinib-treated patients to RWD

The analysis aiming for a direct comparison between RWD and mobocertinib-treated patients does not provide added value. Actually, the provided results confirm the concerns regarding such an analysis. To provide unbiased results, the analysis requires the assumption of no unmeasured confounding, i.e. that all confounding factors are accounted for in the analysis, which is not fulfilled. Indeed, although the RWD from the German Chart Review and the Flatiron Database were aimed to be balanced to the patients from Study 101 regarding baseline factors by weighting, the outcomes in the two RWD sources are substantially different (e.g. ORR 0% in German Chart Review, 12% in Flatiron),

highlighting the difficulties of indirect comparisons. The reasons are unknown; beside residual confounding, differences in treatments or standards of response assessment may be possible. In addition, the considerably larger sample sizes of RWD in the weighted analysis raises the concern that single patients may have a large weight in the analysis such that it may lack robustness.

In vitro biomarker test for patient selection for efficacy

The in-vitro biomarker test(s) used for patient selection for efficacy in the pivotal study AP32788-15-101 is/are insufficienty characterised and lack clarification (OC).

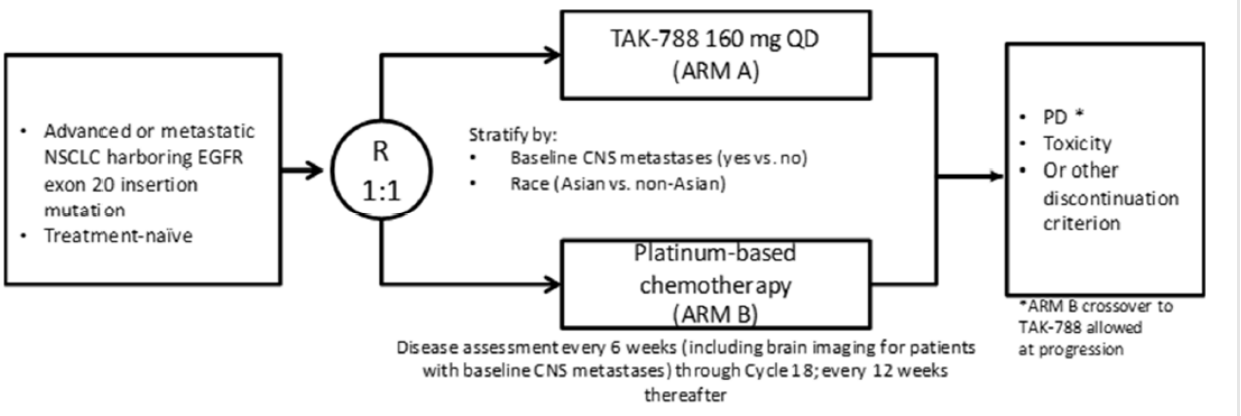
Additional expert consultation

The CHMP considers the SAG Oncology should be consulted with regard to the relevance of the mobocertinib data data to support an indication for the *"treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive advanced non-small cell lung cancer (NSCLC), who have received prior platinum-based therapy"*

Additional efficacy data needed in the context of a conditional MA

If results from pivotal study AP32788-15-101 were considered positive for CMA, the major non-comprehensiveness of data on the efficacy side would stem from the uncertainties with regard to the primary efficacy estimate, ORR.

As confirmatory study and specific obligation (SOB), the applicant proposes the ongoing randomised controlled open-label phase 3 study TAK-788-3001 comparing mobocertinib monotherapy versus a pemetrexed-platinum–based chemotherapy control in patients with treatment-naïve (i.e. 1st-line setting) NSCLC with EGFR exon 20 insertion mutations. The primary endpoint is PFS. The study has been designed to enrol approximately 318 patients. One-way cross-over to the experimental arm is allowed at progression.



Enrolment began January 2020. A futility analysis was conducted based on 127 randomised patients, the recommendation of the IDMC to continue the study as planned indicating that the observed improvement of investigator-assessed best response (confirmation not required) by mobocertinib over chemotherapy exceeded prespecified futility analysis threshold 15%. Enrolment is expected to be completed in third quarter 2022, interim PFS analysis in fourth quarter 2022, final PFS analysis and final OS analysis in fourth quarter 2023. The interim analysis for efficacy is planned after 50% (159 of 318) PFS events will be observed.

Of note, CHMP scientific advice provided in 2019 (before study start) (EMEA/H/SA/3828/1/FU/1/2019/II) did not agree upon the proposed one-way cross-over and the proposed interim analysis for PFS (details of CHMP scientific advice see above section 2.3). However,

as to provided protocol of study TAK-788-3001 (Amendment No 6; date 22 Jan 2021), it is understood that notwithstanding this PFS interim analysis is part of the study protocol and one-way cross-over is performed.

The applicant was asked for clarification, in how far issues raised in the CHMP scientific advice in 2019 (EMEA/H/SA/3828/1/FU/1/2019/II) before study start concerning the interim analysis for efficacy and one-way cross-over are adequately addressed, considering but not limited to the following issues: clinical relevance of expected PFS effect size at IA; data maturity for PFS and for OS; evaluation of long-term PFS effects; in how far can a detrimental effect on OS be excluded; data consistency of relevant subgroups; expected effect on OS evaluation of one-way cross over to mobocertinib after PD.
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The information that was provided by the applicant in this respect is not considered sufficient. It is still not clear whether the time horizon of PFS will be adequately covered at IA and whether sufficient data will be available for an exploratory subgroup analysis. Additionally, it is questionable whether a 3-3.5 months improvement in median PFS, which is the expected effect according to sample size calculation, can be considered as a clinically relevant benefit in this setting. Therefore, mature OS data will be required in this indication with a limited life expectancy, ideally supporting efficacy but minimally allowing reasonable assessment in how far a detrimental effect on OS can be considered unlikely. Interpretation of OS data may be seriously hampered by the possibility for cross-over from chemotherapy to mobocertinib in the protocol for patients randomized to the control arm. The simulations provided by the applicant to estimate the probabilities of OS point estimate HR < 1 at IA and FA under different assumptions on cross-over proportions and on the relationship between response and survival are not helpful regarding the question in how far assessment whether a detrimental effect on OS can be considered unlikely will be possible at IA or FA, as the assumptions are unverifiable and a point estimate of OS HR < 1 alone does not allow excluding a detrimental effect.

Additional information on the expected data maturity at interim analysis and final analysis (with regard to number of OS events, adequate coverage of PFS and OS time horizons) should be provided. However, whether OS (being of particular importance considering that the size of the expected PFS benefit is considered of limited clinical relevance) in spite of cross-over will be interpretable, must remain open until the results of the study are available. (MO)

3.3.6. Conclusions on clinical efficacy

Level of evidence provided by the single pivotal study AP32788-15-101 is considered low. This is based on the facts that study AP32788-15-101 is a multiply analysed, fundamentally amended, uncontrolled, open-label, first-in-human study. Targeted indication in this current MAA is based on a post-hoc defined subpopulation from this study.

This exploratory cORR (IRC) data presented with a low level of evidence, suggest promising clinical activity of mobocertinib monotherapy in the studied population that should be confirmed. The shown effect size of cORR is lower than what could be considered as 'outstanding' (MO). Furthermore, the uncertainties in the efficacy estimate with a low level of evidence of the exploratory data provided make the interpretation challenging.

3.3.7. Clinical safety

Across the 2 mobocertinib clinical studies included in the safety analysis of the applicant, originally a total of 325 patients with advanced cancer and healthy subjects have been enrolled and treated with mobocertinib as of November 2020 data cut-off. The updated ISS (Integrated Summary of Safety) as of November 2021 (data cut-off) refers to 5 safety analysis populations of which the overall safety

population (n = 358) includes all patients who received mobocertinib at least 1 dose of monotherapy at any dose level.

The SCS (summary of clinical safety) focused on the safety findings reported in the extension cohort (Part 3) of trial AP32788-15-101 (in brief 101), patients who received the 160 mg once daily (QD) recommended dose of mobocertinib, and the overall safety population. The analyses of the data from these 3 populations of these 2 trials were considered by the applicant to be the most pertinent and served as the primary evaluation of safety for the application.

Table 1.a below details the clinical studies presented in the submitted SCS. Please note that the applicant did submit an updated ISS but no update of SCS so that table 1.a (as of the original SCS) below provides an overview of Clinical Safety Studies at the datacut-off date November 2020.

Table 1.a Clinical Safety Studies

Study No.	Part	Patient Population	Indication	Dose and Regimen	Accrual Status	No. of Patients Enrolled	Included in the ISS
Study 101	1	Previously treated	NSCLC	Total daily doses explored included 5, 10, 20, 40, 80, 120, 160, and 180 mg	Closed	73 [a]	Yes
	2	Previously treated; treatment naïve	NSCLC	160 mg QD	Closed	137 [a]	Yes
	3	Previously treated	*EGFR* exon 20 NSCLC	160 mg QD	Closed	97 [a]	Yes
TAK-788-1003	1	Previously treated	*EGFR* exon 20 NSCLC	Total daily doses explored included 40, 120, and 160 mg	Closed	20 [b]	Yes
TAK-788-1003	2	Treatment naïve	*EGFR* exon 20 NSCLC	160 mg QD	Ongoing	33 [c]	No
TAK-788-1004	-	Previously treated	NSCLC	160 mg QD [d]	Closed	26 [c]	No
TAK-788-3001	-	Treatment naïve	*EGFR* exon 20 NSCLC	160 mg QD	Ongoing [e]	140 [c]	No

EGFR: epidermal growth factor receptor; ISS: Integrated Summary of Safety; NSCLC: non–small cell lung cancer; QD: once daily.

[a] Patients enrolled as of 01 November 2020.

[b] Patients enrolled as of 31 March 2020.

[c] Patients enrolled as of 15 March 2021.

[d] Cycle 1 includes midazolam administration as well as mobocertinib.

[e] Enrollment is on hold pending the outcome of a futility analysis slated for August 2021.

Table 108.a below provides an overview on the clinical studies included into the updated ISS (SAP v2.0, data cut-off 01 November 2021 (Study 101 Parts 1, 2, and 3) and 08 November 2021 (TAK-788-1003 Parts 1 and 2)) provided in response to safety question 108.

Table 108.a Safety Analysis Populations in the Integrated Summary of Safety

Analysis Population (n)	Definition	Clinical Studies
Overall Safety (n = 358)	All patients who have received at least 1 dose of mobocertinib.	Studies 101 (Parts 1, 2, and 3) and 1003 (Parts 1 and 2)
160 mg QD (n = 290)	All patients who have received at least 1 dose of mobocertinib at 160 mg QD.	Studies 101 (Parts 1, 2, and 3) and 1003 (Parts 1 and 2)
Pretreated (n = 226)	All patients who have been previously treated for locally advanced or metastatic disease and who received at least 1 dose of mobocertinib at 160 mg QD.	Studies 101 (Parts 1, 2, and 3) and 1003 (Part 1)
Pooled Prior Platinum (n = 114)	All patients with metastatic NSCLC with *EGFR* exon 20 insertion mutations who had previously been treated with platinum-based chemotherapy and who received at least 1 dose of mobocertinib at 160 mg QD.	Study 101 (Parts 1, 2, and 3)
Treatment Naïve (n = 64)	All patients in the 160 mg QD population who have not been previously treated for locally advanced or metastatic disease.	Studies 101 (Part 2) and 1003 (Part 2)

EGFR: epidermal growth factor receptor; NSCLC; non–small cell lung cancer; QD: once daily.

Furthermore, safety data from 4 clinical pharmacology trials are mentioned (and submitted as CSR by the applicant) but were not integrated or presented in the SCS, namely TAK-788-1001, TAK-788-1002, TAK-788-1005, and TAK-788-1006. Further ongoing clinical trials of the applicant (to evaluate the effect of severe renal impairment; TAK-788-1007; and moderate or severe hepatic impairment; TAK-788-1008 on the pharmacokinetics (PK) of mobocertinib) are not included in SCS or the ISSs.

The applicant has clarified that safety data of TAK-788-3001 are still not available for integrations whereas safety data of TAK-788-1003 Part 2 have been integraged into the ISS as of November 2021 (compare also table 1.a and 108.a above).

3.3.7.1. Patient exposure

With the ISS cut-off date November 2020 (ISS1), median time on treatment for the study 101 Part 3 overall population was 6.80 months, which was slightly higher than the 160 mg QD population (6.05 months) and the overall population (5.29 months), as outlined in Table 3.b. The applicant explained that a 'study 101 Part 3' population was no longer an analysis population of the ISS with cut-off date November 2021 (ISS2). The corresponding exposure data of the overall 5 analysis populations of the ISS2 are provided in table 108.c below.

Relative median dose intensity was 100% for the Study 101 Part 3 population; and was also 100% in the 160 mg QD population and the overall population (ISS1). For the values resulting from the ISS2, see table 108.c below. Of note, relative median dose intensity in the treatment naïve population (not an analysis population of the ISS1) was 84.6% only. Also notable is the median daily dose intensity of 120.7 mg in this analysis population.

Per ISS2, only 23-32 % of patients were treated with mobocertinib for ≥12 months, and it must be highlighted that long-term safety data is limited.

Table 3.b Patient Study Drug Exposure (All Analysis Populations)

	Mobocertinib		
	Study 101 (Part 3) N = 96	**160 mg QD N = 257**	**Overall N = 325**
Time on study treatment (months) [a]			
Mean (SD)	7.54 (4.712)	7.75 (6.747)	7.16 (6.769)
Median	6.80	6.05	5.29
Minimum, maximum	0.0, 18.8	0.0, 40.3	0.0, 40.3
Duration of exposure, n (%)			
<1 month	6 (6)	26 (10)	45 (14)
1 to <3 months	14 (15)	47 (18)	65 (20)
3 to <6 months	20 (21)	55 (21)	70 (22)
6 to <12 months	31 (32)	65 (25)	73 (22)
≥12 months	25 (26)	64 (25)	72 (22)
Number of days dosed			
Mean (SD)	220.8 (143.19)	224.8 (202.28)	208.1 (202.70)
Median	184.5	168.0	148.0
Minimum, maximum	1, 571	1, 1213	1, 1213
Mobocertinib cumulative dose (mg)			
Mean (SD)	33046.3 (22666.76)	31912.8 (28908.87)	28073.3 (28319.03)
Median	26360.0	23380.0	17,760.0
Minimum, maximum	160, 91360	160, 162720	65, 162720
Mobocertinib dose intensity (mg/day) [b]			
Mean (SD)	141.82 (25.264)	134.28 (29.617)	122.28 (40.457)
Median	157.69	149.68	125.35
Minimum, maximum	65.4, 160.0	38.3, 160.0	4.0, 180.0
Mobocertinib relative dose intensity (%) [c]			
Mean (SD)	92.53 (11.981)	92.11 (21.077)	93.52 (19.923)
Median	100.0	100.00	100.00
Minimum, maximum	53.9, 100.0	29.7, 285.1	29.7, 285.1

Source: ISS Table 18.1.1.5.1 (data cutoff: 01 November 2020).
ISS: Integrated Summary of Safety; QD: once daily.
[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 108.c Patient Study Drug Exposure (All Analysis Populations); ISS2 (November 2021)

	Mobocertinib				
	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
Time on study treatment (months) [a]					
Median	5.88	7.38	7.56	6.49	5.50
Minimum, maximum	0.0, 52.5	0.0, 48.0	0.4, 26.9	0.0, 52.5	0.0, 52.5
Duration of exposure, n (%)					
<1 month	23 (10)	8 (7)	6 (9)	29 (10)	48 (13)
1 to <3 months	43 (19)	17 (15)	7 (11)	50 (17)	68 (19)
3 to <6 months	48 (21)	19 (17)	12 (19)	60 (21)	75 (21)
6 to <12 months	51 (23)	33 (29)	24 (38)	75 (26)	83 (23)
≥12 months	61 (27)	37 (32)	15 (23)	76 (26)	84 (23)
Number of days dosed					
Median	166.0	214.5	207.0	178.0	159.5
Minimum, maximum	1, 1564	1, 1448	8, 789	1, 1564	1, 1564
Mobocertinib cumulative dose (mg)					
Median	22800.0	30480.0	25360.0	23520.0	19020.0
Minimum, maximum	160, 231680	160, 231680	1120, 126240	160, 231680	65, 231680
Mobocertinib dose intensity (mg/day) [b]					
Median	150.84	155.41	120.68	147.69	125.35
Minimum, maximum	38.3, 160.0	65.4, 160.0	52.2, 160.0	38.3, 160.0	4.0, 180.0
Mobocertinib relative dose intensity (%) [c]					
Median	100.00	100.00	84.60	100.00	100.00
Minimum, maximum	29.7, 285.1	51.2, 100.0	44.9, 100.0	29.7, 285.1	29.7, 285.1

Source: ISS Table 18.1.1.5.1 (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).
ISS: Integrated Summary Of Safety; QD: once daily.
[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.

Demographic and other characteristics of ISS/SCS populations

Demographic characteristics were mostly comparable between the 3 analysis populations of ISS1 (see Table 4.a below).

Table 4.a Demographic Characteristics (All Analysis Populations)

	Study 101 Part 3 N = 96	160 mg QD N = 257	Overall N = 325
Age (years)			
Mean (SD)	59.1 (11.69)	60.5 (11.19)	60.6 (11.22)
Median	59.0	61.0	61.0
Min, max	27, 80	24, 86	24, 86
Age categories, n (%)			
18-49 years	20 (21)	45 (18)	55 (17)
50-64 years	41 (43)	115 (45)	142 (44)
65-74 years	27 (28)	72 (28)	99 (30)
75-84 years	8 (8)	23 (9)	27 (8)
≥85 years	0	2 (<1)	2 (<1)
Gender, n (%)			
Male	34 (35)	88 (34)	106 (33)
Female	62 (65)	169 (66)	219 (67)
Ethnicity, n (%)			
Hispanic or Latino	1 (1)	12 (5)	16 (5)
Not Hispanic and Latino	95 (99)	232 (90)	289 (89)
Not Reported	0	13 (5)	20 (6)
Race, n (%)			
Asian	66 (69)	102 (40)	119 (37)
Black or African American	2 (2)	12 (5)	16 (5)
White	28 (29)	140 (54)	182 (56)
Other	0	0	3 (<1)
Not reported	0	3 (1)	5 (2)
Geographic region, n (%)			
Asia Pacific (China, Japan, other)	57 (59)	70 (27)	77 (24)
Europe	10 (10)	10 (4)	10 (3)
North America	29 (30)	177 (69)	238 (73)

Source: ISS Table 18.1.1.2.1 and 18.1.1.2.2 (data cutoff: 01 November 2020).
ISS: Integrated Summary of Safety; QD: once daily.

For the 5 safety populations being subject of the ISS2 (November 2021) see Table 18.1.1.2.1 (module 5 of the dossier) and for the 160 mg QD population Table 110.b (Demographic Characteristics for Patients With or Without Dose Modification limited to the 160 mg QD Population, in the response to q 110)). Note that the study 101 part 3 patients are no longer a separate sub-population of the ISS2 and is incorporated in the other populations as appropriate. The 33 Japanese, treatment naïve patients expand the overall population to 358 patients (Asian n=152). All these 33 additional patients in the ISS2 are also added to the 160 mg QD population (n=290) increasing the proportion of Asians in this subpopulation from 40% to 47%.

Aspects regarding age/sex/race may have implications for safety and are discussed further in section 3.3.7.6 below.

Apart from characterization of oncologic status, the applicant's initial submission did not include a discussion of other medical conditions at baseline in the patient populations. The applicant provided this as a response to Q113 Differences between analysis populations are small and not expected to constitute an issue affecting the characterization of the safety profile of mobocertinib.

3.3.7.2. Adverse events

AEs are analysed and presented by the applicant in terms of TEAEs (treatment emergent AEs) with reference to the ISS (see also below TEAEs and T**R**AEs).

Accordingly, safety evaluations were performed in the ISS1 on the Study 101 Part 3 study population, the 160 mg QD patient population, and the overall safety population, as outlined in Table 5.b.

Table 5.b Overall Summary of TEAEs (All Analysis Populations)

	Mobocertinib		
	Study 101 Part 3 N = 96	160 mg QD N = 257	Overall N = 325
Category of AE	n (%) of Patients		
Any TEAE [a]	96 (100)	257 (100)	323 (99)
Drug-related TEAE	95 (99)	253 (98)	315 (97)
Grade ≥3 TEAE	63 (66)	172 (67)	216 (66)
Drug-related Grade ≥3 TEAE	40 (42)	108 (42)	126 (39)
Treatment-emergent SAE	45 (47)	118 (46)	153 (47)
Drug-related treatment-emergent SAE	17 (18)	43 (17)	52 (16)
TEAE resulting in study drug dose modification [b]	57 (59)	176 (68)	224 (69)
TEAE resulting in study drug discontinuation	10 (10)	48 (19)	67 (21)
TEAE resulting in study drug interruption	48 (50)	158 (61)	201 (62)
TEAE resulting in study drug dose reduction	21 (22)	81 (32)	93 (29)
On-study deaths [c]	8 (8)	29 (11)	43 (13)

Source: ISS Table 18.1.1.10.1 (data cutoff: 01 November 2020).

AE: adverse event; ISS: Integrated Summary of Safety; QD: once daily; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

[a] 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 is counted once for each type of experienced event. Percentages are based on the total number of patients in the safety population. MedDRA Dictionary (Version 23.0) was used for coding AEs.

[b] Modification includes discontinuation, interruption or reduction.

[c] On-study death is defined as the death that occurs between the first dose of any study drug and 30 days after the last dose of any study drug.

The corresponding table for the 5 analysis populations of the ISS2 are provided in table 108.e below.

Table 108.e Overall Summary of TEAEs (All Analysis Populations)

	Mobocertinib				
	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
Category of AE	Number (%) of Patients				
Any TEAE [a]	**226 (100)**	**114 (100)**	**64 (100)**	**290 (100)**	**356 (99)**
Drug-related TEAE	222 (98)	113 (99)	64 (100)	286 (99)	348 (97)
Grade ≥3 TEAE	163 (72)	86 (75)	43 (67)	206 (71)	250 (70)
Drug-related Grade ≥3 TEAE	101 (45)	59 (52)	32 (50)	133 (46)	151 (42)
Treatment-emergent SAE	109 (48)	60 (53)	27 (42)	136 (47)	171 (48)
Drug-related treatment-emergent SAE	36 (16)	22 (19)	13 (20)	49 (17)	58 (16)
TEAE resulting in study drug dose modification [b]	156 (69)	75 (66)	52 (81)	208 (72)	256 (72)
TEAE resulting in study drug discontinuation	39 (17)	21 (18)	13 (20)	52 (18)	71 (20)
TEAE resulting in study drug interruption	139 (62)	64 (56)	52 (81)	191 (66)	234 (65)
TEAE resulting in study drug dose reduction	68 (30)	31 (27)	35 (55)	103 (36)	115 (32)
On-study deaths [c]	31 (14)	15 (13)	4 (6)	35 (12)	49 (14)

Source: ISS Table 18.1.1.10.1 (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).
AE: adverse event; ISS: Integrated Summary of Safety; MedDRA: Medical Dictionary for Regulatory Activities; QD: once daily; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
[a] 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 is counted once for each type of experienced event. Percentages are based on the total number of patients in the safety population. MedDRA Dictionary (Version 24.0) was used for coding AEs.
[b] Modification includes discontinuation, interruption, or reduction.
[c] On-study death is defined as a death that occurs between the first dose of any study drug and 30 days after the last dose of any study drug.

All patients experienced adverse events (except 2 patients) and drug-related AEs (except 10 patients), and two thirds of patients experienced higher grade (≥ grade 3) AEs. The overall incidences of AEs are comparable between the three, and five, safety populations presented in the application.

Overall, there was, and is, a significant overlap across the 3, and 5, safety populations, respectively. Specifically, the pre-treated with platinum-based chemotherapy population is entirely a sub-population of the pre-treated population. In contrast, the pre-treated (n=226) and treatment naïve (n=64) safety populations are two distinct and separate subpopulations of the 160 mg QD population (n=290).

Given that the SCS involves studies that used single-agent mobocertinib, the majority of TEAEs across the safety analysis populations were reported as related to study drug. The rate of TEAEs, including those deemed study drug-related (T**R**AEs) and Grade ≥3, was consistent across the safety populations.

In the first submission, adverse events for the Pooled Prior Platinum Analysis set were only briefly mentioned. Following the response to Q108, this set is now subject of the updated ISS2.

Common AEs

TEAEs

In the ISS1/SCS, the rates of TEAEs (≥10% of patients) in Study 101 Part 3 population were consistent with the additional 2 safety analysis populations.

The most common TEAEs were gastrointestinal (GI) disorders (the most frequently reported events in this System Organ Class [SOC] included diarrhea, 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 Preferred Terms (PTs).

The (updated) ISS2 did not analyse separately a 'study 101 part 3 safety population'. Corresponding values for the overall 5 analysis populations are shown below. For the 290 patients of the 160 mg QD population, the frequencies of SOC 'GI disorders' and 'Skin and subcutaneous tissue disorders' were 98% and 86% respectively, thus, in essence the same as reported for ISS1.

Table 108.y Most Common (Reported in ≥10% Patients in Any Group) TEAEs by SOC and PT (All Analysis Populations)

	Mobocertinib				
SOC PT	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
	Number (%) of Patients				
Patients with any TEAE	**226 (100)**	**114 (100)**	**64 (100)**	**290 (100)**	**356 (99)**
GI disorders	**221 (98)**	**111 (97)**	**64 (100)**	**285 (98)**	**344 (96)**
Diarrhoea	210 (93)	106 (93)	63 (98)	273 (94)	325 (91)
Nausea	106 (47)	46 (40)	36 (56)	142 (49)	171 (48)
Vomiting	88 (39)	49 (43)	18 (28)	106 (37)	121 (34)
Stomatitis	60 (27)	30 (26)	36 (56)	96 (33)	106 (30)
Gastrooesophageal reflux disease	31 (14)	17 (15)	7 (11)	38 (13)	51 (14)
Constipation	27 (12)	16 (14)	10 (16)	37 (13)	45 (13)
Dry mouth	24 (11)	8 (7)	6 (9)	30 (10)	35 (10)
Dyspepsia	21 (9)	13 (11)	5 (8)	26 (9)	30 (8)
Abdominal pain	18 (8)	12 (11)	2 (3)	20 (7)	27 (8)
Mouth ulceration	15 (7)	14 (12)	0	15 (5)	16 (4)
Skin and subcutaneous tissue disorders	**188 (83)**	**105 (92)**	**61 (95)**	**249 (86)**	**291 (81)**
Rash	87 (38)	54 (47)	26 (41)	113 (39)	126 (35)
Dry skin	67 (30)	38 (33)	23 (36)	90 (31)	107 (30)
Dermatitis acneiform	43 (19)	22 (19)	22 (34)	65 (22)	72 (20)
Rash maculo-papular	36 (16)	16 (14)	12 (19)	48 (17)	58 (16)
Pruritus	43 (19)	29 (25)	7 (11)	50 (17)	53 (15)
Alopecia	29 (13)	24 (21)	11 (17)	40 (14)	44 (12)
Investigations	**153 (68)**	**83 (73)**	**47 (73)**	**200 (69)**	**233 (65)**
Blood creatinine increased	69 (31)	40 (35)	17 (27)	86 (30)	93 (26)
Amylase increased	53 (23)	28 (25)	12 (19)	65 (22)	78 (22)
Weight decreased	46 (20)	28 (25)	20 (31)	66 (23)	76 (21)
Lipase increased	41 (18)	23 (20)	16 (25)	57 (20)	64 (18)
Aspartate aminotransferase increased	33 (15)	14 (12)	8 (13)	41 (14)	45 (13)
Lymphocyte count decreased	21 (9)	7 (6)	14 (22)	35 (12)	41 (11)
Alanine aminotransferase increased	26 (12)	12 (11)	9 (14)	35 (12)	40 (11)
Electrocardiogram QT prolonged	26 (12)	21 (18)	9 (14)	35 (12)	39 (11)
Platelet count decreased	22 (10)	13 (11)	4 (6)	26 (9)	31 (9)
Metabolism and nutrition disorders	**145 (64)**	**75 (66)**	**32 (50)**	**177 (61)**	**218 (61)**
Decreased appetite	84 (37)	51 (45)	22 (34)	106 (37)	131 (37)
Hypomagnesaemia	28 (12)	15 (13)	5 (8)	33 (11)	42 (12)
Dehydration	26 (12)	10 (9)	5 (8)	31 (11)	41 (11)

Table 108.y Most Common (Reported in ≥10% Patients in Any Group) TEAEs by SOC and PT (All Analysis Populations)

SOC PT	Mobocertinib Pretreated N = 226	Mobocertinib Pooled Prior Platinum N = 114	Mobocertinib Treatment-Naïve N = 64	Mobocertinib 160 mg QD N = 290	Mobocertinib Overall N = 358
	Number (%) of Patients				
Hypokalaemia	29 (13)	16 (14)	8 (13)	37 (13)	40 (11)
Hyponatraemia	23 (10)	8 (7)	5 (8)	28 (10)	34 (9)
Hypocalcaemia	17 (8)	12 (11)	5 (8)	22 (8)	26 (7)
General disorders and administration site conditions	**135 (60)**	**69 (61)**	**35 (55)**	**170 (59)**	**209 (58)**
Fatigue	57 (25)	24 (21)	17 (27)	74 (26)	95 (27)
Pyrexia	25 (11)	15 (13)	4 (6)	29 (10)	36 (10)
Asthenia	19 (8)	14 (12)	2 (3)	21 (7)	29 (8)
Infections and infestations	**128 (57)**	**72 (63)**	**42 (66)**	**170 (59)**	**202 (56)**
Paronychia	67 (30)	44 (39)	28 (44)	95 (33)	102 (28)
Respiratory, thoracic and mediastinal disorders	**124 (55)**	**71 (62)**	**31 (48)**	**155 (53)**	**199 (56)**
Dyspnoea	41 (18)	19 (17)	6 (9)	47 (16)	64 (18)
Cough	39 (17)	28 (25)	4 (6)	43 (15)	55 (15)
Epistaxis	17 (8)	10 (9)	7 (11)	24 (8)	31 (9)
Rhinorrhoea	24 (11)	17 (15)	6 (9)	30 (10)	31 (9)
Nervous system disorders	**90 (40)**	**36 (32)**	**26 (41)**	**116 (40)**	**144 (40)**
Headache	34 (15)	12 (11)	6 (9)	40 (14)	48 (13)
Dizziness	20 (9)	12 (11)	5 (8)	25 (9)	32 (9)
Dysgeusia	17 (8)	7 (6)	9 (14)	26 (9)	31 (9)
Musculoskeletal and connective tissue disorders	**94 (42)**	**55 (48)**	**22 (34)**	**116 (40)**	**141 (39)**
Back pain	38 (17)	27 (24)	2 (3)	40 (14)	51 (14)
Blood and lymphatic system disorders	**87 (38)**	**51 (45)**	**19 (30)**	**106 (37)**	**121 (34)**
Anaemia	68 (30)	39 (34)	15 (23)	83 (29)	96 (27)
Vascular disorders	**50 (22)**	**24 (21)**	**15 (23)**	**65 (22)**	**79 (22)**
Hypertension	33 (15)	16 (14)	10 (16)	43 (15)	47 (13)
Psychiatric disorders	**34 (15)**	**21 (18)**	**14 (22)**	**48 (17)**	**63 (18)**
Insomnia	15 (7)	10 (9)	7 (11)	22 (8)	27 (8)

Source: ISS Table 18.1.1.13.1 (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).

AE: adverse event; GI: gastrointestinal; ISS: Integrated Summary of Safety; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QD: once daily; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

TEAEs are defined as any AE 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 SOC, and once within each PT. MedDRA Dictionary (Version 24.0) was used for coding AEs.

TRAEs

All 3 safety populations of the ISS1 received single-agent mobocertinib; therefore, the majority of TEAEs were reported as related to study drug (T**R**AE =treatment **related/drug related** AEs). Data were overall comparable across populations. The most common TRAEs (≥10% of patients) were GI disorders (diarrhea, nausea, stomatitis, and vomiting) and skin and subcutaneous tissue disorders (rash and dry skin).

In response to an OC raised (Q114), certain frequent TRAEs that were previously omittied as ADRs in the SmPC have now been included.

Values from the 5 analysis sets based on the updated ISS2 following the latest data cut-off are included in the table below. Data are consistent with what was shown in the first submission (ISS1).

Table 108.z Most Common (Reported in ≥10% of Patients in Any Group) Drug-Related TEAEs by SOC and PT (All Analysis Populations)

	Mobocertinib				
SOC	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
PT	Number (%) of Patients				
Patients with any drug-related TEAE	**222 (98)**	**113 (99)**	**64 (100)**	**286 (99)**	**348 (97)**
GI disorders	**214 (95)**	**108 (95)**	**63 (98)**	**277 (96)**	**330 (92)**
Diarrhoea	207 (92)	105 (92)	62 (97)	269 (93)	315 (88)
Nausea	89 (39)	39 (34)	33 (52)	122 (42)	140 (39)
Stomatitis	56 (25)	28 (25)	34 (53)	90 (31)	99 (28)
Vomiting	65 (29)	36 (32)	15 (23)	80 (28)	91 (25)
Gastrooesophageal reflux disease	26 (12)	14 (12)	5 (8)	31 (11)	37 (10)
Mouth ulceration	14 (6)	14 (12)	0	14 (5)	15 (4)
Skin and subcutaneous tissue disorders	**186 (82)**	**105 (92)**	**59 (92)**	**245 (84)**	**279 (78)**
Rash	86 (38)	53 (46)	24 (38)	110 (38)	120 (34)
Dry skin	62 (27)	35 (31)	22 (34)	84 (29)	97 (27)
Dermatitis acneiform	42 (19)	21 (18)	21 (33)	63 (22)	70 (20)
Rash maculo-papular	35 (15)	16 (14)	12 (19)	47 (16)	56 (16)
Pruritus	37 (16)	25 (22)	6 (9)	43 (15)	46 (13)
Alopecia	23 (10)	18 (16)	7 (11)	30 (10)	34 (9)
Investigations	**117 (52)**	**66 (58)**	**37 (58)**	**154 (53)**	**173 (48)**
Amylase increased	40 (18)	23 (20)	11 (17)	51 (18)	58 (16)
Blood creatinine increased	43 (19)	31 (27)	14 (22)	57 (20)	58 (16)
Lipase increased	36 (16)	23 (20)	14 (22)	50 (17)	55 (15)
Weight decreased	24 (11)	16 (14)	18 (28)	42 (14)	48 (13)
Electrocardiogram QT prolonged	23 (10)	19 (17)	9 (14)	32 (11)	36 (10)
Aspartate aminotransferase increased	24 (11)	9 (8)	6 (9)	30 (10)	32 (9)
Alanine aminotransferase increased	19 (8)	10 (9)	8 (13)	27 (9)	29 (8)
Metabolism and nutrition disorders	**99 (44)**	**56 (49)**	**23 (36)**	**122 (42)**	**144 (40)**
Decreased appetite	63 (28)	42 (37)	19 (30)	82 (28)	100 (28)

Table 108.z Most Common (Reported in ≥10% of Patients in Any Group) Drug-Related TEAEs by SOC and PT (All Analysis Populations)

SOC PT	Mobocertinib Pretreated N = 226	Mobocertinib Pooled Prior Platinum N = 114	Mobocertinib Treatment-Naïve N = 64	Mobocertinib 160 mg QD N = 290	Mobocertinib Overall N = 358
	Number (%) of Patients				
Infections and infestations	84 (37)	48 (42)	33 (52)	117 (40)	128 (36)
Paronychia	66 (29)	43 (38)	28 (44)	94 (32)	101 (28)
General disorders and administration site conditions	**80 (35)**	**41 (36)**	**26 (41)**	**106 (37)**	**126 (35)**
Fatigue	38 (17)	17 (15)	13 (20)	51 (18)	67 (19)
Respiratory, thoracic and mediastinal disorders	**50 (22)**	**32 (28)**	**16 (25)**	**66 (23)**	**78 (22)**
Rhinorrhoea	14 (6)	12 (11)	3 (5)	17 (6)	18 (5)
Blood and lymphatic system disorders	**54 (24)**	**31 (27)**	**15 (23)**	**69 (24)**	**74 (21)**
Anaemia	38 (17)	21 (18)	11 (17)	49 (17)	52 (15)
Nervous system disorders	**36 (16)**	**15 (13)**	**14 (22)**	**50 (17)**	**58 (16)**
Dysgeusia	14 (6)	5 (4)	9 (14)	23 (8)	28 (8)

Source: ISS Table 18.1.1.13.2 (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).
AE: adverse event; ALT: alanine aminotransferase; ISS: Integrated Summary of Safety; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QD: once daily; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
TEAEs are defined as any AE 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 SOC, and once within each PT. MedDRA Dictionary (Version 24.0) was used for coding AEs.

TEAEs Grade ≥3

In the ISS1, the majority of TEAEs in Study 101 Part 3 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 diarrhea being the most frequently reported event.

In addition to diarrhea, other frequently reported Grade ≥3 TEAEs in Study 101 Part 3 (by Medical Dictionary for Regulatory Activities [MedDRA] prefer terms [PT]) were Grade 3 anemia (7%) and hypertension (6%), blood creatinine increased (5%), pneumonia and ECG QT prolonged (4% each).

In the 160 mg QD population, the most frequently reported Grade 3 TEAEs in addition to diarrhea (19%) were Grade 3 anemia and hypertension (7% each), dyspnea, lipase increased, and stomatitis (4% each). Anemia and hypertension (6% each), and dyspnea and amylase increased (4% each) were also common Grade 3 TEAEs for the overall safety population. Seven (7%) patients in Part 3 had Grade 4 events, with 3% of the events from cardiac disorders SOC.

Overall, Grade 4 TEAEs occurred in 7% of 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 across all 3 safety populations were consistent with the disease under study (see subsequent section death).

The same considerations apply for the 5 safety populations of the updated ISS2 (see table 108.h below).

Table 108.aa TEAEs Grade ≥3 (Reported in ≥5 Patients Within a Safety Population) by PT (All Analysis Populations)

	Mobocertinib				
	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
PT	Number (%) of Patients				
Patients with at least 1 TEAE	**163 (72)**	**86 (75)**	**43 (67)**	**206 (71)**	**250 (70)**
Diarrhoea	46 (20)	27 (24)	14 (22)	60 (21)	66 (18)
Anaemia	15 (7)	7 (6)	2 (3)	17 (6)	21 (6)
Hypertension	16 (7)	8 (7)	4 (6)	20 (7)	21 (6)
Pneumonia	13 (6)	5 (4)	1 (2)	14 (5)	19 (5)
Dyspnoea	12 (5)	6 (5)	1 (2)	13 (4)	18 (5)
Amylase increased	9 (4)	6 (5)	2 (3)	11 (4)	15 (4)
Electrocardiogram QT prolonged	11 (5)	9 (8)	3 (5)	14 (5)	15 (4)
Lipase increased	11 (5)	5 (4)	3 (5)	14 (5)	15 (4)
Lymphocyte count decreased	6 (3)	3 (3)	6 (9)	12 (4)	15 (4)
Hyponatraemia	7 (3)	2 (2)	1 (2)	8 (3)	12 (3)
Nausea	9 (4)	6 (5)	1 (2)	10 (3)	12 (3)
Dehydration	5 (2)	2 (2)	3 (5)	8 (3)	11 (3)
Stomatitis	7 (3)	5 (4)	2 (3)	9 (3)	10 (3)
ALT increased	3 (1)	1 (<1)	5 (8)	8 (3)	9 (3)
Hypokalaemia	7 (3)	4 (4)	2 (3)	9 (3)	9 (3)
Hypoxia	6 (3)	2 (2)	0	6 (2)	9 (3)
NSCLC	6 (3)	3 (3)	1 (2)	7 (2)	9 (3)
Respiratory failure	6 (3)	3 (3)	0	6 (2)	9 (3)
Acute kidney injury	6 (3)	3 (3)	2 (3)	8 (3)	8 (2)
Blood creatinine increased	8 (4)	5 (4)	0	8 (3)	8 (2)
Decreased appetite	5 (2)	2 (2)	3 (5)	8 (3)	8 (2)
Neoplasm progression	3 (1)	1 (<1)	0	3 (1)	8 (2)
Vomiting	6 (3)	4 (4)	1 (2)	7 (2)	8 (2)
Back pain	5 (2)	2 (2)	0	5 (2)	7 (2)
Hypophosphataemia	4 (2)	2 (2)	1 (2)	5 (2)	7 (2)
Pulmonary embolism	3 (1)	1 (<1)	2 (3)	5 (2)	7 (2)
Asthenia	2 (<1)	1 (<1)	0	2 (<1)	6 (2)
Fatigue	4 (2)	3 (3)	1 (2)	5 (2)	6 (2)
Weight decreased	1 (<1)	1 (<1)	5 (8)	6 (2)	6 (2)
Abdominal pain	3 (1)	2 (2)	0	3 (1)	5 (1)
Hypotension	3 (1)	2 (2)	1 (2)	4 (1)	5 (1)
Pericardial effusion	4 (2)	3 (3)	1 (2)	5 (2)	5 (1)
Pleural effusion	3 (1)	2 (2)	0	3 (1)	5 (1)

Table 108.aa TEAEs Grade ≥3 (Reported in ≥5 Patients Within a Safety Population) by PT (All Analysis Populations)

	Mobocertinib				
	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
PT	Number (%) of Patients				
Thrombocytopenia	2 (<1)	1 (<1)	1 (2)	3 (1)	5 (1)

Source: ISS Table 18.1.1.13.7 (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).
AE: adverse event; ALT: alanine aminotransferase; ISS: Integrated Summary of Safety; NSCLC: non—small cell lung cancer; PT: Preferred Term; QD: once daily; TEAE: treatment-emergent adverse event.
TEAEs are defined as any AE that occurs from the first dose of study drug and until 30 days after the last dose of study drug.

3.3.7.3. Serious adverse events, deaths, and other significant events

SAEs

Treatment-Emergent SAEs

Data based on the first data cut-off showed that treatment-emergent SAEs occurred in 46-47% of patients as outlined in Table 5.g below. The most common treatment-emergent SAEs (ie, dyspnea and diarrhea) were consistent across the 3 study populations.

Table 5.g Most Common (Reported in ≥2% of Patients in Any Group) Treatment-Emergent SAEs by SOC and PT (All Analysis Populations)

SOC PT	Mobocertinib Study 101 Part 3 N = 96	Mobocertinib 160 mg QD N = 257	Mobocertinib Overall N = 325
	n (%) of Patients		
Patients with any treatment-emergent SAE	**45 (47)**	**118 (46)**	**153 (47)**
Respiratory, thoracic, and mediastinal disorders	**8 (8)**	**29 (11)**	**40 (12)**
Dyspnoea	5 (5)	16 (6)	21 (6)
Respiratory failure	1 (1)	4 (2)	7 (2)
GI disorders	**11 (11)**	**31 (12)**	**39 (12)**
Diarrhoea	5 (5)	13 (5)	15 (5)
Vomiting	4 (4)	12 (5)	14 (4)
Nausea	1 (1)	5 (2)	7 (2)
Infections and infestations	**6 (6)**	**22 (9)**	**31 (10)**
Pneumonia	1 (1)	10 (4)	15 (5)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**7 (7)**	**19 (7)**	**29 (9)**
Metastases to CNS	3 (3)	3 (1)	4 (1)
NSCLC	2 (2)	5 (2)	7 (2)
Neoplasm progression	0	3 (1)	8 (2)
Cardiac disorders	**6 (6)**	**12 (5)**	**14 (4)**
Pericardial effusion	2 (2)	3 (1)	3 (<1)
General disorders and administration site conditions	**6 (6)**	**16 (6)**	**16 (5)**
Pyrexia	4 (4)	5 (2)	5 (2)
Metabolism and nutrition disorders	**5 (5)**	**11 (4)**	**16 (5)**
Dehydration	3 (3)	6 (2)	10 (3)
Decreased appetite	2 (2)	3 (1)	3 (<1)
Renal and urinary disorders	**4 (4)**	**10 (4)**	**10 (3)**
Acute kidney injury	2 (2)	8 (3)	8 (2)

Source: ISS Table 18.1.1.13.5 (data cutoff: 01 November 2020).
CNS: central nervous system; ISS: Integrated Summary of Safety; GI: gastrointestinal; NSCLC: non—small cell lung cancer; PT: Preferred Term; QD: once daily; SAE: serious adverse event; SOC: System Organ Class.

Following the latest cut-off, data from the latest ISS show that 42-53 % of patients had a treatment-emergent SAE, with 47 % reported in 160 mg QD population. Incidences are, overall and by PTs, consistent with previously reported data. However, hypoxia is now included in the list of most common serious events (2 %, see below).

Table 108.bb Most Common (Reported in ≥2% of Patients in Any Group) Treatment-Emergent SAEs by SOC and PT (All Analysis Populations)

SOC PT	Mobocertinib Pretreated N = 226	Mobocertinib Pooled Prior Platinum N = 114	Mobocertinib Treatment-Naïve N = 64	Mobocertinib 160 mg QD N = 290	Mobocertinib Overall N = 358
	Number (%) of Patients				
Patients with any treatment-emergent SAE	**109 (48)**	**60 (53)**	**27 (42)**	**136 (47)**	**171 (48)**
GI disorders	**27 (12)**	**19 (17)**	**8 (13)**	**35 (12)**	**43 (12)**
Diarrhoea	12 (5)	9 (8)	2 (3)	14 (5)	16 (4)
Vomiting	11 (5)	7 (6)	2 (3)	13 (4)	15 (4)
Nausea	6 (3)	4 (4)	0	6 (2)	8 (2)
Respiratory, thoracic, and mediastinal disorders	**29 (13)**	**13 (11)**	**3 (5)**	**32 (11)**	**43 (12)**
Dyspnoea	15 (7)	8 (7)	2 (3)	17 (6)	22 (6)

Table 108.bb Most Common (Reported in ≥2% of Patients in Any Group) Treatment-Emergent SAEs by SOC and PT (All Analysis Populations)

	Mobocertinib				
SOC PT	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
	Number (%) of Patients				
Respiratory failure	6 (3)	3 (3)	0	6 (2)	9 (3)
Hypoxia	5 (2)	2 (2)	0	5 (2)	6 (2)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**22 (10)**	**11 (10)**	**2 (3)**	**24 (8)**	**34 (9)**
NSCLC	6 (3)	3 (3)	1 (2)	7 (2)	9 (3)
Neoplasm progression	3 (1)	1 (<1)	0	3 (1)	8 (2)
Metastases to CNS	4 (2)	3 (3)	0	4 (1)	5 (1)
Infections and infestations	**19 (8)**	**9 (8)**	**5 (8)**	**24 (8)**	**33 (9)**
Pneumonia	9 (4)	2 (2)	3 (5)	12 (4)	17 (5)
Metabolism and nutrition disorders	**10 (4)**	**4 (4)**	**7 (11)**	**17 (6)**	**22 (6)**
Dehydration	4 (2)	2 (2)	2 (3)	6 (2)	10 (3)
Decreased appetite	4 (2)	2 (2)	3 (5)	7 (2)	7 (2)
General disorders and administration site conditions	**15 (7)**	**9 (8)**	**1 (2)**	**16 (6)**	**16 (4)**
Pyrexia	5 (2)	4 (4)	0	5 (2)	5 (1)
Renal and urinary disorders	**9 (4)**	**5 (4)**	**3 (5)**	**12 (4)**	**12 (3)**
Acute kidney injury	7 (3)	3 (3)	3 (5)	10 (3)	10 (3)

Source: ISS Table 18.1.1.13.5 (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).
AE: adverse event; CNS: central nervous system; ISS: Integrated Summary of Safety; GI: gastrointestinal; MedDRA: Medical Dictionary for Regulatory Activities; NSCLC: non—small cell lung cancer; PT: Preferred Term; QD: once daily; SAE: serious adverse event; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
TEAEs are defined as any AE 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 SOC, and once within each PT. MedDRA Dictionary (Version 24.0) was used for coding AEs.

Treatment-Related SAEs

Data from the ISS based on the first cutoff showed that treatment-related SAEs occurred in 16-18% of patients, with diarrhoea and vomiting as the most common events, which is outlined in Table 5.h below.

Table 5.h Most Common (Reported in ≥2% of Patients in Any Group) Treatment-Related SAEs by SOC and PT (All Analysis Populations)

SOC / PT	Mobocertinib n (%) of Patients: Study 101 Part 3 N = 96	160 mg QD N = 257	Overall N = 325
Patients with any treatment-related SAE	**17 (18)**	**43 (17)**	**52 (16)**
GI disorders	**9 (9)**	**21 (8)**	**24 (7)**
Diarrhoea	4 (4)	11 (4)	13 (4)
Vomiting	4 (4)	10 (4)	11 (3)
Metabolism and nutrition disorders	**3 (3)**	**7 (3)**	**9 (3)**
Dehydration	2 (2)	5 (2)	6 (2)
Renal and urinary disorders	**3 (3)**	**6 (2)**	**6 (2)**
Acute kidney injury	2 (2)	5 (2)	5 (2)

Source: ISS Table 18.1.1.13.6 (data cutoff: 01 November 2020).
GI: gastrointestinal; ISS: Integrated Summary of Safety; PT: Preferred Term; QD: once daily; SAE: serious adverse event; SOC: System Organ Class.

Data based on the latest cutoff (ISS2) are overall consistent with what was initially reported. Treatment-related SAE occur in 16-20 % of patients, and is unchanged at 17 % in the 160 mg QD population. Diarrhoea and vomiting are still the most commonly reported PTs (see the table below):

Table 108.cc Most Common (Reported in ≥2% of Patients in Any Group) Treatment-Related SAEs by SOC and PT (All Analysis Populations)

SOC / PT	Mobocertinib Number (%) of Patients: Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
Patients with any treatment-related SAE	**36 (16)**	**22 (19)**	**13 (20)**	**49 (17)**	**58 (16)**
GI disorders	18 (8)	13 (11)	5 (8)	23 (8)	26 (7)
Diarrhoea	10 (4)	7 (6)	2 (3)	12 (4)	14 (4)
Vomiting	8 (4)	5 (4)	2 (3)	10 (3)	11 (3)
Nausea	5 (2)	3 (3)	0	5 (2)	5 (1)
Metabolism and nutrition disorders	**5 (2)**	**3 (3)**	**4 (6)**	**9 (3)**	**11 (3)**
Dehydration	3 (1)	2 (2)	2 (3)	5 (2)	6 (2)
Decreased appetite	1 (<1)	1 (<1)	2 (3)	3 (1)	3 (<1)
Renal and urinary disorders	**4 (2)**	**3 (3)**	**2 (3)**	**6 (2)**	**6 (2)**
Acute kidney injury	3 (1)	2 (2)	2 (3)	5 (2)	5 (1)

Source: ISS Table 18.1.1.13.6 (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).
AE: adverse event; GI: gastrointestinal; ISS: Integrated Summary of Safety; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QD: once daily; SAE: serious adverse event; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
TEAEs are defined as any AE 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 SOC, and once within each PT. MedDRA Dictionary (Version 24.0) was used for coding AEs.

A discussion of pyrexia, dehydration and acute kidney injury, which are adverse events that appear to be serious in some patients, was requested in the D120 LoQ (Q114). In the response, the applicant has provided a dissussion and agreed to include AKI and dehydration as ADRs. Inclusion of pyrexia as an ADR in the product information is still requested (subject of SmPC OC).

Deaths

According to the ISS1, on-study deaths occurred in 8% of the Study 101 Part 3 population, which is similar to the number of on-study deaths in the 160 mg QD population (11%) and the overall population (13%). 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 (narratives are provided in the Study 101 CSR Section 15.3.3). Remaining on-study deaths were not related to study drug but related to the underlying disease (i.e. neoplasm progression and NSCLC).

Following CSR TAK-788-1003, a single event of deaths within 30 days of last dose occurred (defined as between administration of the first dose and 30 days after the last dose, or initiation of subsequent anticancer therapy) was reported in 1 patient at 120 mg QD. The death occurred on Day 42, and the last dose of study drug (80 mg) was taken on Day 26. No drug-related death was reported in trial 1003.

Following the updated ISS2, on-study deaths, occurred in 12% (n = 35) of patients in the 160 mg QD population, consistent with the previously reported 11 %.

Deaths assessed as related to the study drug occurred in 2 patients (<1%) in this population and included deaths due to respiratory failure and cardiac failure, both of which were described in the initial SCS and the AP32788-15-101 CSR, Section 15.3.3. The remaining on study deaths were not related to study drug but related to the underlying disease (ie, neoplasm progression and NSCLC).

Other Significant TEAEs leading to dose modification, reduction, drug interruption or discontinuation

The frequencies of TEAEs leading to drug interruption/dose reduction/study discontinuation was originally higher in the overall population (62%/29%/21%) and the 160 mg QD population (61 %/32 %/19%) compared to the Study 101 Part 3 population (50 %/22 %/10 %), where the mean dose intensity was also higher (142 mg). The CHMP concluded that **dose modifications** (both interruptions and reductions) occurred less frequently in the Study 101 Part 3 population than in the other safety populations.

With reference to the updated 160 mg QD population (n= 290 patients at the November 2021 data cut-off), the applicant explained that that **dose modifications** overall were frequent (n=208 patients; 72%). The most common dose modification due to a TEAE was dose **interruption**, which occurred in 191 patients (66%). Less frequent were TEAE leading to **dose reductions** (103 patients; 36%).

The number of patients who **discontinued** study drug due to a TEAE was relatively low (52 patients; 18%).

Concerning the change in the safety analysis populations (ISS1/SCS vs. ISS2), the percentage of patients having TEAEs leading to study drug interruption, dose reduction, and discontinuation were similar (56%-66%, 27%-36%, and 17%-20%, respectively) across 4 of the safety populations analyzed according to SAP v.2 (pretreated, prior platinum, 160 mg QD, and overall).

In the (new) treatment-naïve analysis sub-group, percentages of drug interruption and dose reduction because of TEAEs were higher than the other safety groups; 81% of patients in this group had study drug interruption and 55% dose reduction (discontinuation after interruption and/or reduction: 9.6%). The treatment-naïve subgroup has a smaller sample size (N = 64) and has a large portion of patients (N = 33) from Japanese Study 1003. Concerning these differences in the new safety sub-population

(naïve), the applicant is of the opinion that a definitive cause is impossible to identify. Data from ongoing study 3001 will provide more information to address this question.

Concerning the originally conducted exposure-safety analyses (not including data of study 1003 part 1 and 2) the applicant explained that no statistically significant relationship was identified between time-averaged exposure and the occurrence of diarrhea, nausea, paronychia, rash, stomatitis, and vomiting. However, based on the final exposure-safety models (295 patients enrolled in Parts 1, 2, and 3 of Study 101 who received QD doses of mobocertinib ranging from 5 mg to 180 mg), a decrease in systemic exposure corresponding to a dose reduction from 160 mg to 120 mg resulted in odds ratios for each TEAE that were less than 1, indicating trends towards a lower probability of TEAEs with lower exposure. In addition, an analysis of Grade ≥3 TEAEs demonstrated a statistically significant relationship with time-averaged exposure (p-value <0.05). The estimated odds ratio associated with a decrease in time-averaged exposure corresponding to a dose reduction from 160 mg to 120 mg QD mobocertinib indicated that a dose reduction is expected to decrease the odds of experiencing Grade ≥3 TEAEs by approximately 30% (odds ratio of 0.701).

Because dose interruptions due to TEAEs occurred overall more frequently than dose reductions (summarizing term "**modification**"), the question arises now whether 120 mg QD is overall the more optimal starting dose for avoiding too many dose modifications (interruption, dose reduction after interruption, dose reduction without interruption) after start of treatment with 160 mg QD due to TEAEs. This question is most evident for the new naïve safety analysis population, a population being also subject of study 3001 currently not included in the safety data base.

In addition, it should be noted that the frequency of patients without event resolution after dose interruption or reduction (=**modification**) is generally high, i.e. the majority (>50%) of TEAEs occurring did not resolve after dose modification (see in particular legend of table 110.a below).

Table 110.dd TEAEs Resolution and Drug Discontinuation After Dose Reduction or Interruption (All Analysis Populations)

	Mobocertinib				
	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment -Naïve N = 64	160 mg QD N = 290	Overall N = 358
Category of AE	Number (%) of Patients				
Number of patients with dose interruption or reduction	147 (65.0)	70 (61.4)	52 (81.3)	199 (68.6)	242 (67.6)
Number of patients with event resolution [a,d] after dose interruption or reduction	67 (45.6)	36 (51.4)	22 (42.3)	89 (44.7)	107 (44.2)
Number of patients without event resolution [b,d] after dose interruption or reduction	80 (54.4)	34 (48.6)	30 (57.7)	110 (55.3)	135 (55.8)
Number of patients with discontinuation [c,d] after dose interruption or reduction	7 (4.8)	4 (5.7)	5 (9.6)	12 (6.0)	21 (8.7)

Source: ISS Table 23.1.1.18.3 (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).
AE: adverse event; QD: once daily; TEAE: treatment-emergent adverse event.
[a] With resolution refers to patients with all AEs that lead to dose reduction/interruption resolved after dose reduction/interruption.
[b] Without resolution means the patient had at least 1 AE that leads to dose reduction/interruption not resolved after dose reduction/interruption.
[c] Patients without AE resolution after dose reduction/interruption and discontinued treatment due to the AE that initially led to dose reduction/interruption.
[d] Percentage is calculated based on the number of patients with dose interruption/reduction.

This raises again the question as to the scientific rational of table 2 of the SmPC entitled: *Recommended Exkivity dose **modifications** and management for adverse reactions. The* CHMP has raised a new OC accordingly comprising also a question concerning the the overall B/R (i.e. analysing also cORR in relation of **modified** and **unmodified** starting dose of 160 mg QD) of the 160 mg starting dose recommended, that may be downtitrated both postmarketing and after occurance of TEAEs (**OC)**.

AEs of Clinical Interest

SCS states that AEs of clinical interest 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/ILD, GI events, skin events, cardiac events, and stomatitis);

3) AEs reported within the mobocertinib program (eg, amylase/lipase increases). The AEs of clinical interest selected for further presentation are pneumonitis/ILD, cardiac disorders, GI toxicities (diarrhea, nausea, vomiting), stomatitis, skin-related events, and amylase/lipase increases. The search strategy for the selected AEs of clinical interest is presented in Table 5.i.

Table 5.i 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
GI toxicities	PTs: diarrhea, 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; HLT: High Level Term; ILD: interstitial lung disease; PT: Preferred Term; SMQ: Standardised MedDRA Query; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

Eye disorders is an identified risk associated with several EGFR-TKIs, indicating a class effect. A discussion of eye disorders was requested in the D120 LoQ, and an acceptable discussion was provided as a response to Q116. Ocular toxicity was reported in 13-17 % of patients (160 mg QD: 15 %), with related TEAEs reported in 6-11 % (160 mg QD: 9 %). The most commonly reported PTs in the SOC eye disorders were dry eye (160 mg QD: TEAE 5 %, TRAE: 3 %), vision blurred (3 %/ 1 %) and blepharitis (2 %/2 %). No cases of keratitis have been reported. The applicant has suggested to add "Ocular toxicity" as and ADR in the SmPC (12 %) with an explanatory footnote. The applicant's approach is considered adequate.

AEs of clinical interest are summarized (in the SCS and the ISS2) by relatedness, grade, seriousness, and discontinuation for each of the 3 safety populations in Table 5.j as of the SCS and table 108.m for ISS2 below.

Table 5.j TEAEs of Clinical Interest – Overall, Relatedness, Grade, Seriousness, Discontinuation (by Safety Population)

	Study 101 Part 3 N = 96	160 mg QD Population N = 257	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)	8 (2)
Cardiac disorders			
TEAE	37 (39)	86 (33)	109 (34)
Related	15 (16)	31 (12)	36 (11)
Grade ≥3	13 (14)	33 (13)	41 (13)
Serious	10 (10)	28 (11)	36 (11)
Discontinued	1 (1)	5 (2)	9 (3)
GI toxicities			
TEAE	91 (95)	247 (96)	302 (93)
Related	91 (95)	242 (94)	291 (90)
Grade ≥3	19 (20)	56 (22)	63 (19)
Serious	8 (8)	22 (9)	27 (8)
Discontinued	4 (4)	18 (7)	22 (7)

	Study 101 Part 3 N = 96	160 mg QD Population N = 257	Overall N = 325
	n (%) of Patients		
Stomatitis			
TEAE	43 (45)	90 (35)	102 (31)
Related	41 (43)	84 (33)	94 (29)
Grade ≥3	3 (3)	9 (4)	10 (3)
Serious	0	0	0
Discontinued	1 (1)	2 (<1)	2 (<1)
Skin-related events			
TEAE	87 (91)	220 (86)	263 (81)
Related	87 (91)	216 (84)	251 (77)
Grade ≥3	6 (6)	12 (5)	12 (4)
Serious	0	0	1 (<1)
Discontinued	0	4 (2)	4 (1)
Amylase/Lipase Increased			
TEAE	69 (72)	186 (72)	229 (70)
Related	58 (60)	154 (60)	182 (56)
Grade ≥3	10 (10)	30 (12)	37 (11)
Serious	8 (8)	19 (7)	23 (7)
Discontinued	3 (3)	11 (4)	12 (4)

Source: ISS Table 18.1.1.16.1A, 18.1.1.16.1B, and 18.1.1.16.1C.

AE: adverse event; 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.

Table 108.ee TEAEs of Clinical Interest – Overall, Relatedness, Grade, Seriousness, Discontinuation (by Safety Population)

	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
	Number (%) of Patients				
Pneumonitis/ILD					
TEAE	6 (3)	2 (2)	5 (8)	11 (4)	15 (4)
Related	3 (1)	1 (<1)	3 (5)	6 (2)	9 (3)
Grade ≥3	2 (<1)	1 (<1)	0	2 (<1)	5 (1)
Serious	4 (2)	1 (<1)	0	4 (1)	7 (2)
Discontinued	3 (1)	1 (<1)	4 (6)	7 (2)	10 (3)
Cardiac disorders					
TEAE	85 (38)	50 (44)	22 (34)	107 (37)	130 (36)
Related	33 (15)	26 (23)	13 (20)	46 (16)	51 (14)
Grade ≥3	35 (15)	23 (20)	8 (13)	43 (15)	51 (14)
Serious	25 (11)	15 (13)	5 (8)	30 (10)	38 (11)
Discontinued	5 (2)	5 (4)	4 (6)	9 (3)	13 (4)
GI toxicities					
TEAE	217 (96)	109 (96)	63 (98)	280 (97)	335 (94)
Related	213 (94)	107 (94)	62 (97)	275 (95)	324 (91)
Grade ≥3	52 (23)	31 (27)	15 (23)	67 (23)	74 (21)
Serious	21 (9)	15 (13)	3 (5)	24 (8)	29 (8)
Discontinued	12 (5)	8 (7)	2 (3)	14 (5)	18 (5)

Table 108.ee TEAEs of Clinical Interest – Overall, Relatedness, Grade, Seriousness, Discontinuation (by Safety Population)

	Pretreated N = 226	Pooled Prior Platinum N = 114	Treatment-Naïve N = 64	160 mg QD N = 290	Overall N = 358
	Number (%) of Patients				
Stomatitis					
TEAE	76 (34)	45 (39)	36 (56)	112 (39)	124 (35)
Related	71 (31)	43 (38)	34 (53)	105 (36)	115 (32)
Grade ≥3	7 (3)	5 (4)	2 (3)	9 (3)	10 (3)
Serious	0	0	0	0	0
Discontinued	2 (<1)	2 (2)	0	2 (<1)	2 (<1)
Skin-related events					
TEAE	193 (85)	106 (93)	61 (95)	254 (88)	297 (83)
Related	191 (85)	106 (93)	59 (92)	250 (86)	285 (80)
Grade ≥3	11 (5)	5 (4)	3 (5)	14 (5)	14 (4)
Serious	0	0	0	0	1 (<1)
Discontinued	3 (1)	1 (<1)	0	3 (1)	3 (<1)
Amylase/lipase increased					
TEAE	169 (75)	88 (77)	45 (70)	214 (74)	257 (72)
Related	139 (62)	74 (65)	40 (63)	179 (62)	207 (58)
Grade ≥3	30 (13)	18 (16)	7 (11)	37 (13)	44 (12)
Serious	18 (8)	13 (11)	4 (6)	22 (8)	26 (7)
Discontinued	6 (3)	4 (4)	1 (2)	7 (2)	8 (2)

Source: ISS Table 18.1.1.16.1A, 18.1.1.16.1B, 18.1.1.16.1C, 18.1.1.16.1D, and 18.1.1.16.1E (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).
AE: adverse event; ILD: interstitial lung disease; ISS: Integrated Summary of Safety; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
TEAEs are defined as any AE 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 SOC, and once within each PT. MedDRA Dictionary (Version 24.0) was used for coding AEs.

Time-to-onset of TEAEs of clinical interest are summarized in a tabulated version in the ISS. Information on time-to-onset and time to resolvement for the AESIs have been included in the SmPC, following a response to the D120 LoQ (Q115)

In terms of methods, 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.

In terms of results, SCS information in addition to table 5.j (both of SCS and as quoted above) concerns the following (abbreviated by Rapp., updates for ISS2 given in {brackets; reference is table 108.m}):

Pneumonitis/ILD

The rates of the AEs of clinical interest of pneumonitis/ILD were similar across the 3 {5} safety populations (2%-4%{2-8%; highest in the new treatment naïve subpopulation}) (see Table 5.j). The most common event within this AEs of clinical interest category was pneumonitis (1% to 3% of patients). Median time-to-onset ranged from 48 to 63 days (160 mg QD updated: 85 days) across the

3 safety populations with the median time to resolution of 2.93 (160 mg QD) to 15.21 (Part 3) weeks (ISS).

> A patient was enrolled into the 120 mg QD dose. On Cycle 1 Day 9, the patient was hospitalized for Grade 4 pneumonitis and study drug was interrupted. Relevant medical history included intermittent cough, hemoptysis, multilobar pneumonia, scattered wheeze, respiratory infection, and mycoplasma pneumonia. The patient had documented metastases to the liver, brain, bone, peritoneum and spinal cord (leptomeningeal) at the time of study entry. She had previously been treated with 2 lines of chemotherapy (carboplatin +pemetrexed) and afatinib. Mobocertinib treatment was initiated 15 days after completion of afatinib treatment. On Cycle 1 Day 9, the patient had TEAEs of rash (Grade 1, assessed by the investigator as unrelated to study drug), anaemia (Grade 3, assessed by investigator as related; note hemoglobin was Grade 1 at study entry), and thrombocytopenia (Grade 4, assessed by investigator as related; platelet count was within normal limits at study entry).
>
> No blood transfusion was given for the anaemia or thrombocytopenia. Study drug was stopped on Cycle 1 Day 9 and the patient died of pneumonitis on Cycle 1 Day 15. The investigator considered the event of pneumonitis possibly related to the study drug and considered the patient's underlying condition of NSCLC stage 4 as another possible cause for these events.

Pneumonitis/ILD is a known class-effect of EGFR-TKIs. This constitutes an important safety issue, and ILD appears to be reported more frequently with mobocertinib than certain other EGFR-TKIs. Compared to TKIs dacomitinib (0.5 %) and afatinib (1.6 %), the incidence of ILD is higher with mobocertinib (up to 4 %), but comparable to osimertinib (3.7 %).

Cardiac disorders (including QTc-interval prolongation)

The search strategy for the cardiac disorders AEs of clinical interest is conservatively broad and the SMQs (Standardised MedDRA Query) used in this search include both cardiac and respiratory SOC terminology. With this search strategy 33% to 39% {34-44%} of patients across all 3 {5} populations reported a TEAE within the cardiac disorders AEs of clinical interest. According to the ISS1, the only event reported in more than 10% of patients was dyspnea (18% to 19% {16% in the 160 mg QD population}), which is a nonspecific event and does not necessarily reflect a cardiac problem.

According to the updated ISS2, another TEAE by PT that was reported in >10% of patients in the 160 mg QD population was ECG QT prolonged (12%) (ISS Table 18.1.1.16.1B, November 2021). This is an increase compared with the November 2020 ISS1, in which 8% of patients had ECG QT prolonged (ISS Table 18.1.1.16.1B, November 2020). In the pooled prior platinum population of the ISS2, 18% of patients had ECG QT prolonged.

Time-to-onset across the AEs of clinical interest of cardiac disorders ranged from a median time-to-onset of 79 to 82 days across the 3 safety populations; a median time to resolution of 1.86 to 2.0 weeks (ISS). Data from the 160 mg QD population based on the latest cutoff was a median TTO of 84 days and a median time to resolution of 2.4 weeks.

Overall, in all 3 safety populations, the majority of events were Grade 1 or 2 (86%-87%), were non-serious (89% to 90%), not drug related (84%-89%), and patient discontinuation from the study because of cardiac disorders was low (≤3%) (Table 5.j).

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 was assessed as related to mobocertinib.

Following the ISS2, a total of 10% of patients in the 160 mg population had serious cardiac disorders. The SAEs that occurred in more than 1 patient were dyspnoea (6%), cardiac failure (1%), and chest pain (1%). One SAE of ventricular arrhythmia was reported to be associated with Torsades de pointes, was assessed as treatment related, and led to discontinuation of mobocertinib. No new cases of ventricular arrhythmia were reported.

A total of 3% of patients in the 160 mg population discontinued study drug due to cardiac disorders. The most frequent TEAEs that led to discontinuation in more than 1 patient were dyspnoea (1%) and cardiac failure (1%).

Three patients died due to TEAEs in the cardiac disorders AEs of clinical interest category. The TEAEs leading to death were cardiac failure (2 patients; <1%) and cardiac arrest (1 patient; <1%). One death was assessed as treatment related: cardiac failure.

A separate unblinded data monitoring committee (DMC) for Study 101 evaluated the results of safety analyses and made recommendations to the applicant as needed. One recommendation from the DMC was enhanced cardiac monitoring (such as left ventricular ejection fraction assessment by echocardiogram [ECHO] or multiple gated acquisition scans); this recommendation is consistent with similar drugs in this class. The assessments were added to new and ongoing studies; they were not added to Study 101, given Study 101 had already completed enrollment and patients had been on study for a median >8 months at the time of the recommendation.

Most of the events in the AESI "cardiac disorders" were classified as lower grade, non-serious and not related to treatment; however, there are some serious events noted. The fatal event of cardiac failure occurred in a patient with a history of cardiovascular complications including cardiac failure that was worsened by mobocertinib.

In ISS1 a case of cardiac failure congestive had 210 days TTO and a case of cardiomyopathy had TTO of 645 days. Even if most AEs in this class debut early, serious events may manifest late. Long-term safety data for mobocertinib is very limited, with only 84 patients exposed for $\geqslant$ 12 months as of the latest cutoff date (Nov 2021). This imposes an uncertainty to the estimated frequency of serious cardiac events as ADRs, which may be higher.

The cardiotoxicity of EGFR HER2-inhibitors, such as laptatinib, is well-described. However, these are indicated for breast cancer. Of the EGFR TKIs indicated for NSCLC (afatinib, dacomitinib, osimertinib and erlotinib) only osimertinib include a warning on cardiac toxicity in SmPC section 4.4 (QTc prolongation, cardiac contractility).

QTc-interval prolongation

There were no new TEAEs of QT prolongation as of ISS2 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, and led to discontinuation of mobocertinib and is described in more detail in the summary section narratives of events of interest of the SCS.

QTc interval prolongation occurs frequently (8 %, updated numbers: 11-18 %, 12 % in the 160 mg QD) in mobocertinib-treated patients, including a case of TdP, which was deemed related. Data on QT-prolongation are from the Study 101, which are included in the cardiac safety report and show that a moderate QT prolonging effect (15 to 20 ms) was demonstrated at doses ≥120 mg. In light of findings from the non-clinical studies, the extent of QTc-prolongation in mobocertinib-treated patients was unexpected.

The risk of QTc prolongation is known to be higher in female patients and patients with higher age (> 65 years),. ISS2 data for the 160 mg QD group show that age (<65; $\geq$ 65 years) can currently not be

considered as a risk factor for QTc prolongation (frequencies similar: 13% vs. 11%) but female patient are at higher risk than males (15% vs. 6%).

For mobocertinib, the SmPC lists QTc prolongation (8 %, updated: 12 %) and cardiac failure (2.3 %, updated 3.4 %) as ADRs and includes warnings on cardiac failure and QTc prolongation, also stating that life-threatening and fatal cases has been reported.

The cardiac toxicity profile of mobocertinib appears more severe than for other TKIs in the class. This is worrisome, and the increased incidence of QTc prolonagation and cardiac failure seen in ISS2 following the latest cutfoff date is of great concern. However, the SmPC includes explicit information in both 4.4 and 4.8. In light of the possibly severe cardiac toxicity profile of mobocertinib, an OC was raised to recommend conducting cardiac monitoring and periodic ECG measurements in all patients, which the applicant agreed to in the response. It is thus considered that the severity of these adverse events is adequately described according to current knowledge, and that the feasible risk minimization measures have been implemented.

GI toxicities

The majority of patients reported an AE of clinical interest of GI toxicity (ie, diarrhoea, nausea, and vomiting) within each of the 3 safety populations (see Table 5.j), with diarrhoea being the most common of these events. Median time-to-onset for AEs of clinical interest GI toxicity events was 5 days in each of the 3 safety populations, with a majority of events resolving in less than 1 week (ie, median time to resolution 0.29-0.50 weeks) (ISS1).

A majority of AEs of clinical interest GI toxicity events were considered related to study dosing, and were Grade ≤2; 8% to 9% of patients experienced a serious event. AEs of clinical interest GI toxicities leading to discontinuation of study dosing was experienced by 4% to 7% of patients. ISS2 is not more informative.

Diarrhoea

A majority of TEAEs in the AEs of clinical interest of GI toxicity were diarrhea. Diarrhea 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 (ISS). Five percent of patients experienced a serious event of diarrhea, leading to drug discontinuation in 2-5 % of patients across populations. The majority of diarrhea events resolved in less than 1 week (ie, median time to resolution 0.14-0.43 weeks). Antidiarrheal medications were frequently dosed for symptom management; the most common agent used was loperamide.

Nausea/Vomiting

Nausea and vomiting symptoms were the second most common AEs of clinical interest GI toxicities reported in the 3 safety analysis populations (any event of nausea or vomiting: 34%-47% , patients experiencing an event deemed related to study drug dosing ranged from 26% to 28% for vomiting; and 30% to 40% for nausea (ISS). The majority of events were Grade 1 or 2 and the number of patients experiencing an event that resulted in dose discontinuations was 1% to 2%. The rate of patients experiencing a serious event of vomiting was 4% to 5% (nausea ≤2%) in each of the safety analysis populations (ISS). The most common concomitant medications for symptomatic management of nausea and/or vomiting included omeprazole, ondansetron, and metoclopramide.

The time-to-onset for nausea or vomiting was within the first few weeks. Nausea tended to linger longer than vomiting, with a median time to resolution 2.21 to 3.14 weeks, whereby vomiting resolved within a week.

Possible clinical sequelae of AEs of clinical interest GI toxicities such has diarrhea, nausea, and vomiting may include dehydration, electrolyte imbalance, and impact on the renal system.

Dehydration was reported in 9-13 % of patients and was reported as a related SAE in 2 % of patients.Dehydration has been added as an ADR (11 %, grade 3: 2.8 %) as a response to Q114 in the D120 LoQ. Electrolyte imbalance (mineral and electrolyte analyses) was noted in 3% to 5% of patients across the 3 safety populations (ISS), which was disussed by the applicant in the response and is now appropriately refleced in the product information (D120 LoQ Q121).

Elevations in creatinine ranged from 25% to 35% of patients in the 3 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 (CSR 101 Part 3: 35% vs 37%; Overall: 29% vs 23%; 160 mg QD: 32% vs 27% [+ISS, Asian vs non-Asian population]; subgroup analyses by race: ISS).

In summary, GI toxicity events, including diarrhea, vomiting, and nausea, are among the most frequently reported TEAEs for mobocertinib, similar to other EGFR TKIs, as these are mechanism-related. AEs of clinical interest GI toxicity events were predominately low grade, with few events deemed serious or resulting in discontinuation of mobocertinib.

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 (29%-43% {as TEAE: 34-56%}) (see Table 5.j {and table 108.m}).

None of these events were deemed serious.

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 AEs of clinical interest (see Table 5.i).

A majority of patients in each of the safety populations had TEAEs that were skin-related (see Table 5.j). Of the skin-related AEs of clinical interest, most were deemed related to study dosing and were Grade 1 to 2 (Grade ≥3: 4%-6% {4-6%}) (Table 5.j {and table 108.m}). Few events (≤2%) led to discontinuation of study dosing and 1 event was deemed serious (Table 5.j). No severe cutaneous events (ie, Stevens-Johnson syndrome or epidermal necrolysis) were observed across the mobocertinib clinical program.

SJS/TEN, however, have been reported for other EGFR TKIs, indicating a class effect. Safety data for mobocertinib is limited, and an OC was raised to ensure that the risk of skin-related events is properly addressed in the SmPC. This was discussed by the applicant in the response to Q117 in the D120 LoQ, and the current product information is considered adequate based on current available knowledge. It is highlighted that MAH's have an obligation to update the product information at all times if new information related to SJS/TEN arise from post-marketing data.

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.

Amylase/lipase Increase

The broad SMQ for acute pancreatitis was used in the ISS to examine elevations of amylase/lipase as pancreatitis has been reported with other EGFR TKIs.

Though 70% to 72% of patients had an event using this AEs of clinical interest search methodology, the majority of the events reported were nausea and vomiting (36%-47% and 34%-37%, respectively across populations) and not necessarily related to amylase/lipase increase (see previous Nausea/Vomiting section for further details).

In the overall safety population, an increase in amylase and/or lipase was reported in 20% and 15% of patients, respectively) (ISS1) {ISS2: In the 160 mg QD population, an increase in amylase and/or lipase was reported in 22% and 20% of patients, respectively}.

Still using the broad SMQ, events associated with this AE of clinical interest 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 (see Table 5.j). No patient developed clinical pancreatitis while on-study.

Median time-to-onset for AEs of clinical interest events of amylase/lipase increase ranged from 15 to 21 days {ISS2: 15.0 days in the 160 mg QD population}, median time to resolution of was 2.14 to 3.64 weeks (ISS) {ISS2: median 2.29 weeks}.

In all 3 safety populations, patient discontinuation because of an AE of clinical interest associated with amylase/lipase increase was low (≤4% {ISS2: <=4%}).

In addition, the SCS adds the following methodological information:

Narratives were generated for patients with the following events:

- Deaths ≤30 days after the last dose of study drug.
- SAEs ≤30 days after the last dose of study drug.
- Discontinuations of study drug due to AEs and not due to disease progression.
- AEs of clinical interest.

The narratives are provided in the CSRs for Study 101 and Study TAK-788-1003 Part 1.

Of note, no cases of pancreatitis were reported during the mobocertinib clinical program in ISS1. Pancreatitis has been reported for other EGFR-TKIs, but is listed as an ADR (uncommon) only for the EGFR-TKIs (with NSCLC indication) gefitinib and afatinib. ISS2 reports on one patient having acute pancreatitis, which was a Grade ≥3 SAE.

3.3.7.4. Laboratory findings and vital signs

The SCS provided analysis of laboratory findings (exclusively with reference to Study 101 and the tabulated ISS).

Vital signs

Vital sign results were only presented in the individual CSRs. The applicant was requested to present an integrated analysis of vital signs from the different analysis population, including the Pooled platinum population, which was provided in the response (D120 LoQ Q113). The most common baseline medical condition was hypertension (30 – 48 %), which is not unexpected in this patient group. Other frequently reported medical conditions at baseline (cough, dyspnoea, fatigue) are associated with the underlying malignant disease. Overall, differences between analysis populations are small and not expected to constitute an issue affecting the characterization of the safety profile of mobocertinibHaematology

Apart from anaemia, which is proposed as an ADR with very common frequency, no discussion on changes in hematologic values was included in the initial application.

From the first ISS, there were reports of drug-related thrombocytopenia (4 %), leukopenia (2 %) and neutropenia (2 %) in the 160 mg QD analysis population. Further, decreases in the levels of lymphocytes, leukocytes, neutrophils and platelets (in addition to hemoglobin) was noted during the first cycles of mobocertinib treatment. After cycle 15 the number of remaining patients was too low to draw conclusions.

The applicant was therefore asked to provide an overview of shifts in blood cell levels/hematologic parameters during treatment and discuss relation to treatment and the need to update the SmPC. Data provided in the response show a high frequency of reported shifts (updated data in the 160 mg QD group): haemoglobin (65%), lymphocyte count (53%), platelet count (29%), and white blood cell count (24%), including higher-grade shifts. This information has been now added as ADRs in the SmPC.

Clinical chemistry

In Study 101, grade ≥3 shifts were observed for alanine aminotransferase (ALT) (4 patients), albumin (2 patients), alkaline phosphatase (1 patient), amylase (13 patients), aspartate aminotransferase (AST) (4 patients), bilirubin (1 patient), creatinine (4 patients), lipase (10 patients), magnesium (2 patients), potassium (4 patients), and sodium (1 patient) No numbers are given for the 160 mg QD or overall safety populations, but it is referred that shifts were similar.

Grade ≥3 shifts are reported in the overall safety population for creatinine (2 %), potassium (4 %), glucose (< 1 %), sodium (1 %), magnesium (2 %), amylase (10 %), lipase (8 %), ALP (< 1 %), bilirubin (< 1 %), AST (1 %) and ALT (2 %). Changes in amylase, lipase, ALT, AST and creatinine are listed as ADRs in 4.8 and are, as such, sufficiently described. Changes in ALP and glucose are not listed, but occur infrequently, so this is accepted.

Electrolyte disturbances are common in mobocertinib-treated patients and may be of higher grade, which was seen in the original submission. In the response, the applicant discussed consequences of electrolyte imbalance. All grade laboratory shifts/grade ≥3 shifts of hypokalaemia (160 mg QD updated: 28%/5%), hyponatraemia (26%/5%), and hypomagnesaemia (30%/2%) as ADRs in the SmPC. Further, dehydration and AKIs has also been added as ADRs. The risk is now appropriately reflected in the SmPC.

Hepatobiliary

Increases in transaminases and bilirubin are reported for several EGFR-TKIs, some of which include warnings on hepatotoxicity in SmPC 4.4 (such as dacomitinib and gefitinib). Increases in hepatic enzyme parameters were commonly reported with mobocertinib (initial/updated numbers in 160 mg QD, AST increased: 23 %/ 25 %, ALT increased 24 %/25 %), as are grade ≥3 shifts (AST 2 %/2 %, ALT 2%/3 %). ALT and AST increased are adequately listed in SmPC 4.8. Treatment-related bilirubin increase reported in the 160 mg QD group was 2 %/3 %, which is not listed as an ADR in the SmPC.

As of the latest cutoff date, no case of severe liver toxicity has been described in the mobocertinib clinical program. One patient presented with hepatotoxicity consistent with Hy's law. This was concluded by the investigators to be unrelated to treatment, which is accepted by the assessors.

The high prevalence of increased liver enzymes raised a concern, and the applicant was asked to discuss whether additional information in the SmPC (warning in 4.4. and advice on monitoring) could be useful. Following the response to this question, the applicant has added a section on liver enzymes to the SmPC 4.8c. With minor revisions, this is considered to address this concern appropriately (subject to SmPC OC).

3.3.7.5. In vitro biomarker test for patient selection for safety

N/A

3.3.7.6. Safety in special populations

Section 8 (safety in special groups and situations) of the SCS submitted provided a relatively comprehensive display of the incidence of TEAEs by SOC and PT by intrinsic (ie, age, sex, race) and extrinsic (region) factors for all (predefined) 3 analysis populations.

The tables presented analyses of:

1. ages 18 to <65 vs. ⩾65 Years
2. males vs. females
3. Asian vs. non-Asian
4. North-America + Europe vs. Asia

Age

For the 160 mg QD population, 63 % of patients are < 65 years, and the median age is 61 years. Thus, more data is available for the patient group < 65 years.

The occurrence of many AEs is comparable across age groups. However, patients with higher age are more prone to experience ≥ grade 3 adverse events (77 % vs 61 %) and serious adverse events (56 % vs 40 %). These numbers are from the 160 mg QD population. In Study 101 Part 3 the differences are even larger (89 % vs 52 % and 66 % vs 36 %, respectively). Patients ≥ 65 years experienced grade ≥ 3 diarrhea more often (160 mg QD: 28 % vs 15 %), which may be of concern.

Additionally, it is of note that amylase increase is reported in 26 % {29%} of patients ≥ 65 years compared to 17 % {18%} of patients < 65 years (160 mg QD population).

The applicant has updated (and discussed) the data for the 160 mg QD population (290 patients, 176 patients below the age of 65, 114 patients 65 years of age or older; for details see table 111.a in the response document). Although the numbers are slightly different, the information is in essence the same: Grade ≥ 3 and serious AEs were more frequent for the older patients (80% vs. 65% and 54% vs. 42%) mainly due to more frequent grade > 3 diarrhea (26% vs. 17%). The applicant proposes to mention the latter in the SmPC.

Biological sex

Roughly two-thirds of patients in the included studies are female. While the overall pattern of AEs is similar in both sexes, it appears that females are more prone to grade ≥ 3 AEs (160 mg QD, females: 70 % vs males: 60 %). Gastrointestinal TEAE occur more frequently in females vs males (number in percent from the 160 mg QD population): nausea (50 vs 41), decreased appetite (39 vs 28), vomiting (44 vs 25), GERD (17 vs 13), and dehydration (15 vs 6). Grade ≥3 diarrhea is reported more often in women (25 vs 10).

Focusing on related TEAEs, the differences for most AEs are negligible between sexes, but related (number in percent from the 160 mg QD population) stomatitis (30 vs 22), alopecia (14 vs 5), and dehydration (10 vs 5) are notably more common in females. Thus, there seem to be a trend that females have a higher risk of experiencing certain AEs than men.

The applicant has updated (and discussed) the data for the 160 mg QD population (290 patients, 100 male patients, 190 female patients;. In essence, the (updated) conclusion of the applicant, while there were some differences in TEAEs between male and female patients, Grade ≥3 TEAEs and SAEs by individual PTs were generally similar, and no clinically significant differences were identified, is valid.

Genetic ancestry

The patients included in the mobocertinib clinical program are divided in "Asians" and "Non-Asians". These groups are assumed to be heterogeneous, but this division provides useful information to a certain extent.

The majority of participants in Study 101 Part 3 are Asians (69 %), and Asians constitute 40 % of 160 mg QD population. While regional variances in which PTs (e.g. mouth ulceration, fatigue) are utilized when AEs are reported during clinical trials may explain some of the differences noted between Asians and Non-Asians, several AEs are reported with higher frequencies in the Asian population.

With reference to table 8.c of the SCS (heading: "TEAEs Occurring in >10% of Patients in Any Group by PT for Intrinsic Factor: Race (All Analysis Populations)") the frequency of **serious** AEs was 26 (**39%**) vs. 19 (**63%**) in the 66 Asian and 30 non-Asian patients investigated in Study 101 Part 3. This pattern, i.e. higher frequency of serious AEs in non-Asian (or regions North-America+Europe) vs. Asian patients was obvious if not significant in all analyses presented for race and/or region. This difference was not subject of the SmPC but the applicant was requested for discussion:

For related TEAEs (Asians/Non-Asians, number in percent from 160 mg QD), the assessors noticed originallyi substantial differences for paronychia (45/17), dry skin (35/23), stomatitis (36/20), blood creatinine increased (25/14), amylase increased (26/8), weight decreased (20/7), lipase increased (22/9), rhinorrhea (13/2), mouth ulceration (14/0) and QT prolongation (13/3). Dehydration (1/13), rash maculopapular (9/20) and fatigue (12/24) are related TEAEs more prevalent in the Non-Asian patient population. The number of reported grade ≥ 3 AEs are also higher in Non-Asian patients (74 % vs 57 % in Asians).

The applicant has updated (and discussed) the data for the 160 mg QD population (**287** patients, 135 Asian patients, 152 non-Asian patients; 3 genetic ancestry not reported; for details see table 111.c below).

The conclusion of the applicant concerning this analysis highlighting by genetic ancestry as to TEAEs and SAEs can overall be followed explaining higher rates in non-Asian patients mainly by diarrhea. Of note, the frequency and severity of QT prolongations is overall higher in the Asian population. This is marked green in table 111.c below).

Table 111.c TEAEs Occurring in ≥10% of Patients in Any Group by PT for Intrinsic Factor: Race (160 mg QD Population)

	Mobocertinib 160 mg QD Number (%) of Patients									
	All Grades	Related	Grade ≥3	Serious	DC	All Grades	Related	Grade ≥3	Serious	DC
PT	Asian (N = 135)					Non-Asian (N = 152)				
Patients with any TEAE	**135 (100)**	**134 (99)**	**89 (66)**	**56 (41)**	**20 (15)**	**152 (100)**	**149 (98)**	**115 (76)**	**79 (52)**	**32 (21)**
Diarrhoea	128 (95)	128 (95)	22 (16)	2 (1)	1 (<1)	142 (93)	138 (91)	38 (25)	12 (8)	9 (6)
Paronychia	69 (51)	68 (50)	1 (<1)	0	0	26 (17)	26 (17)	0	0	0
Nausea	61 (45)	57 (42)	5 (4)	2 (1)	1 (<1)	79 (52)	63 (41)	5 (3)	4 (3)	3 (2)
Rash	59 (44)	58 (43)	0	0	0	53 (35)	51 (34)	1 (<1)	0	1 (<1)
Stomatitis	59 (44)	57 (42)	3 (2)	0	1 (<1)	36 (24)	32 (21)	6 (4)	0	1 (<1)
Decreased appetite	53 (39)	45 (33)	7 (5)	6 (4)	1 (<1)	52 (34)	36 (24)	1 (<1)	1 (<1)	2 (1)
Dry skin	52 (39)	49 (36)	1 (<1)	0	0	38 (25)	35 (23)	0	0	0
Vomiting	46 (34)	40 (30)	3 (2)	6 (4)	1 (<1)	59 (39)	39 (26)	4 (3)	7 (5)	3 (2)
Blood creatinine increased	44 (33)	35 (26)	4 (3)	1 (<1)	0	42 (28)	22 (14)	4 (3)	2 (1)	0
Amylase increased	43 (32)	38 (28)	6 (4)	1 (<1)	0	21 (14)	12 (8)	5 (3)	0	0
Weight decreased	40 (30)	32 (24)	4 (3)	0	0	25 (16)	10 (7)	2 (1)	1 (<1)	1 (<1)
Anaemia	38 (28)	26 (19)	6 (4)	0	0	43 (28)	21 (14)	11 (7)	3 (2)	0
Lipase increased	38 (28)	35 (26)	6 (4)	1 (<1)	0	17 (11)	13 (9)	7 (5)	0	0
Dermatitis acneiform	32 (24)	32 (24)	1 (<1)	0	0	32 (21)	30 (20)	2 (1)	0	0
Electrocardiogram QT prolonged	27 (20)	26 (19)	12 (9)	0	0	8 (5)	6 (4)	2 (1)	0	0
Alopecia	25 (19)	19 (14)	0	0	0	15 (10)	11 (7)	0	0	1 (<1)
Cough	24 (18)	2 (1)	0	0	0	19 (13)	3 (2)	0	0	0
Hypertension	23 (17)	8 (6)	10 (7)	0	0	20 (13)	3 (2)	10 (7)	0	0
Pruritus	23 (17)	22 (16)	1 (<1)	0	0	26 (17)	20 (13)	0	0	0
ALT increased	22 (16)	19 (14)	6 (4)	0	0	12 (8)	7 (5)	2 (1)	1 (<1)	0
AST increased	20 (15)	16 (12)	2 (1)	0	0	20 (13)	13 (9)	1 (<1)	0	0
Fatigue	20 (15)	14 (10)	2 (1)	0	0	53 (35)	36 (24)	3 (2)	1 (<1)	1 (<1)
Pyrexia	20 (15)	7 (5)	0	3 (2)	0	9 (6)	1 (<1)	1 (<1)	2 (1)	0
Dyspnoea	19 (14)	2 (1)	4 (3)	7 (5)	1 (<1)	28 (18)	2 (1)	9 (6)	10 (7)	2 (1)

Table 111.c TEAEs Occurring in ≥10% of Patients in Any Group by PT for Intrinsic Factor: Race (160 mg QD Population)

	Mobocertinib 160 mg QD Number (%) of Patients									
	All Grades	Related	Grade ≥3	Serious	DC	All Grades	Related	Grade ≥3	Serious	DC
PT	Asian (N = 135)					Non-Asian (N = 152)				
Constipation	18 (13)	2 (1)	1 (<1)	0	0	19 (13)	4 (3)	0	1 (<1)	0
Rhinorrhoea	18 (13)	14 (10)	0	0	0	12 (8)	3 (2)	0	0	0
Back pain	17 (13)	1 (<1)	0	0	0	23 (15)	3 (2)	5 (3)	4 (3)	0
Dysgeusia	17 (13)	16 (12)	0	0	0	9 (6)	7 (5)	0	0	0
Gastrooesophageal reflux disease	17 (13)	14 (10)	0	0	0	21 (14)	17 (11)	1 (<1)	1 (<1)	0
Headache	16 (12)	4 (3)	0	0	0	24 (16)	4 (3)	0	0	0
Rash maculo-papular	16 (12)	16 (12)	0	0	0	32 (21)	31 (20)	4 (3)	0	1 (<1)
Hypokalaemia	15 (11)	7 (5)	5 (4)	0	0	22 (14)	11 (7)	4 (3)	0	1 (<1)
Insomnia	15 (11)	3 (2)	0	0	0	7 (5)	1 (<1)	0	0	0
Lymphocyte count decreased	15 (11)	7 (5)	6 (4)	0	0	19 (13)	8 (5)	6 (4)	0	0
Mouth ulceration	15 (11)	14 (10)	0	0	0	0	0	0	0	0
Platelet count decreased	15 (11)	12 (9)	1 (<1)	1 (<1)	1 (<1)	11 (7)	9 (6)	2 (1)	0	0
White blood cell count decreased	14 (10)	10 (7)	1 (<1)	0	0	6 (4)	6 (4)	0	0	0
Dry mouth	10 (7)	10 (7)	0	0	0	20 (13)	16 (11)	0	0	0
Dyspepsia	10 (7)	9 (7)	0	0	0	16 (11)	11 (7)	0	0	0
Hypomagnesaemia	10 (7)	6 (4)	1 (<1)	0	0	23 (15)	8 (5)	0	0	0
Muscle spasms	9 (7)	6 (4)	0	0	0	16 (11)	7 (5)	0	0	0
Mucosal inflammation	8 (6)	8 (6)	0	1 (<1)	0	17 (11)	16 (11)	0	0	0
Blood alkaline phosphatase increased	7 (5)	3 (2)	0	0	0	17 (11)	2 (1)	0	0	0
Dehydration	4 (3)	1 (<1)	1 (<1)	1 (<1)	0	27 (18)	20 (13)	7 (5)	5 (3)	1 (<1)

Source: ISS Table 18.1.1.12.3B (data cutoff: Study 101, 01 November 2021; Study 1003, 08 November 2021).

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DC: discontinuation; ECG: electrocardiogram; ISS: Integrated Summary of Safety; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QD: once daily; TEAE: treatment-emergent adverse event.

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. DC means AE resulting in study drug discontinuation. A patient reporting the same event more than once has that event counted only once within each PT.

Table 111.c TEAEs Occurring in ≥10% of Patients in Any Group by PT for Intrinsic Factor: Race (160 mg QD Population)

	Mobocertinib 160 mg QD Number (%) of Patients									
	All Grades	Related	Grade ≥3	Serious	DC	All Grades	Related	Grade ≥3	Serious	DC
PT	Asian (N = 135)					Non-Asian (N = 152)				

Patients with 1 or more AEs within a level of MedDRA term are counted only once in that level. MedDRA Dictionary (Version 24.0) was used for coding AEs. Patients who have race reported as "not reported" are excluded from analysis.

Drug Interactions

Drug interactions with the strong cytochrome P-450 (CYP)3A inhibitor itraconazole and the strong CYP3A inducer rifampin were evaluated in clinical Study TAK-788-1006. A physiologically-based PK analysis was also performed to characterize the drug-drug interaction profile of mobocertinib

In addition, a drug-drug interaction study evaluating the effect of mobocertinib on the PK of midazolam Study TAK-788-1004 has been completed.

For more details, see Pharmacokinetic interaction studies in sec. 3.3.1.2 Pharmacokinetics of this assessment report.

Use in Pregnancy and Lactation

As of the data cutoff of 01 November 2021, no cases of pregnancy were reported in any of the safety analysis populations.

In Study TAK-788-1004 (not included in the ISS safety analysis population), a patient's partner reported pregnancy 5 weeks post the last dose of mobocertinib. No associated AEs were reported regarding this pregnancy.

There is 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.

For more details, see also sec. 3.2 (non-clinical) and 3.4 (RMP) of this AR.

Overdose

No overdoses reported in the safety population. No specific antidote is available for overdose with mobocertinib. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

Drug Abuse

No systematic examination of the abuse potential of mobocertinib was performed in the nonclinical and clinical studies included in this submission. There is no information regarding the dependence potential in animals or humans. Evaluation of AEs does not reveal evidence of euphoria, sedation, or mood alteration.

Withdrawal and Rebound

No studies or systematic analyses to evaluate the potential withdrawal and rebound effects of mobocertinib have been conducted.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the effects on the ability to drive and use machines have been performed. If patients experience symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Exposure-Safety Analyses

Exposure-safety analyses were performed to evaluate the relationship between systemic exposures and the following AEs: diarrhea, nausea, paronychia, rash, stomatitis, and vomiting (Module 2.7.2). No statistically significant relationship was identified between mobocertinib exposure and the occurrence of any of these AEs; however, the final exposure-safety models suggested a reduction in the odds of experiencing these TEAEs as the odds ratios associated with a change in exposure corresponding to a dose reduction from 160 mg to 120 mg were less than 1.

In addition, no statistically significant relationship was identified between mobocertinib systemic exposures and the time to the first dose reduction. These findings, taken together with the results of the exposure-efficacy analyses (Module 2.7.2 and Module 2.7.3), support the conclusion of a favorable benefit-risk profile of the proposed dosing regimen of mobocertinib 160 mg QD.

With reference to sec. 3.3.1.2 (pharmacodynamics) of this AR, however, the applicant was asked to further justify the expected effectiveness of dose reductions in response to adverse events in an individual patient. To allow further understanding if dose reductions, interruptions, or dose modifications in general could be effective in reducing the severity of a TEAE in an individual patient, the applicant was requested to provide an analysis that states the percentage of patients with dose reductions that were able to continue the therapy after dose reduction without ongoing/resuming adverse events vs. patients that needed to finally stop the treatment because of ongoing/resuming adverse events.

Based on the final exposure-safety models (295 patients enrolled in Parts 1, 2, and 3 of Study 101 who received QD doses of mobocertinib ranging from 5 mg to 180 mg) submitted in response, a decrease in systemic exposure corresponding to a dose reduction from 160 mg to 120 mg resulted in odds ratios for each TEAE that were less than 1, indicating trends towards a lower probability of TEAEs with lower exposure. In addition, an analysis of Grade ≥3 TEAEs demonstrated a statistically significant relationship with time-averaged exposure (p-value <0.05). The estimated odds ratio associated with a decrease in time-averaged exposure corresponding to a dose reduction from 160 mg to 120 mg QD mobocertinib indicated that a dose reduction is expected to decrease the odds of experiencing Grade ≥3 TEAEs by approximately 30% (odds ratio of 0.701).

The question arises now whether 120 mg QD is overall the more optimal starting dose for avoiding too many dose modifications (interruption, dose reduction after interruption, dose reduction without interruption) after start of treatment with 160 mg QD due to TEAEs. This question is most evident for the new naïve safety analysis population comprising all new naïve Japanese patients (as of study 1003), a population being also subject of study 3001 which currently not included in ISS

In addition, it should be noted that the frequency of patients without event resolution after dose interruption or reduction (=**modification**) is generally high, i.e. the majority (>50%) of TEAEs occurring did not resolve after dose modification (see table 110.a in section 3.2.7.3).

This raises again the question as to the scientific rational of table 2 of the SmPC entitled: *Recommended Exkivity dose **modifications** and management for adverse reactions.* The CHMP has raised a new OC for clarification of the labelling of sec. 4.2 of the SmPC (**OC)**.

3.3.7.7. Immunological events

N/A

3.3.7.8. Safety related to drug-drug interactions and other interactions

The SCS states that CYP3A inducer rifampin were evaluated in clinical Study TAK-788-1006. A physiologically-based PK analysis was also performed to characterize the drug-drug interaction profile of mobocertinib. In addition, a drug-drug interaction study evaluating the effect of mobocertinib on the PK of midazolam (Study TAK-788-1004) has been performed.

3.3.7.9. Discontinuation due to adverse events

The frequency of dose discontinuation of study drug due to a TEAE was reported to be 10% to 21% in the SCS, with the most common cause for discontinuation being GI disorders.. The range of

discontinuation due to AEs is from ISS2is in the range of 17% to 20% in the overall 5 safety analysis sets (20% overall and 18% in the 160 mg QD population).

3.3.7.10. Post marketing experience

On September 15, 2021, the Food and Drug Administration granted accelerated approval to mobocertinib (Exkivity, Takeda Pharmaceuticals, Inc.). There is still no marketing experience reported in module 1 of the dossier of this procedure for the market EU.

3.3.8. Discussion on clinical safety

According to the applicant the clinical safety data available as of November 2020 (update as of November 2021 in {presented in brackets}) indicate that mobocertinib has overall an acceptable and manageable safety profile. The data for the 160 mg QD (N = 257 patients {290 patients}) and the overall safety analysis populations (N = 325 patients {358 patients}) also support the safety profile of mobocertinib at 160 mg QD, similar to Part 3 of Study 101. The TEAEs are consistent and generally expected on the basis of nonclinical and early clinical studies with mobocertinib, as well as mechanism-related TEAEs.

Although this view can be shared in general, the safety database is, however, currently rather limited.

Studies originally included in the analysis of safety (SCS/ISS1)

The present MAA application is claiming approval of 160 mg mobocertinib QD for the treatment of NSCLC with EGFR exon 20 insert mutations in patients who have undergone platinum-based therapy. Safety data from the clinical development program include patients from the uncontrolled SAT TAK-788-1003 and three parts of the closed AP32788-15-101 (Study 101) where the part 3 extension with 96 previously treated patients ("101-3") is the main study supporting the indication.

The other analysis populations presented in the original SCS were the 160 mg QD population (n = 257, patients who have received at least one dose of 160 mg mobocertinib, abbreviated "160 mg QD") and the overall safety population (n = 325, patients who have received any dose of mobocertinib). Safety information presented in the SmPC is, and was, mainly based on data from the 160 mg QD population. At data lock-point (Nov 2020), 50 patients were ongoing on treatment in overall population (101-3: 25, 160 mg QD: 49), and it must be highlighted that long-term safety data is strictly limited.

The pooled prior platinum (PPP) analysis set (n = 114) consists of previously platinum-treated patients from all three parts of Study 101 who have received at least one dose of 160 mg mobocertinib. The applicant noted that safety data are consistent across all patient groups. The applicant did not present the PPP population in the in-text tables in ISS1, however, the safety findings were summarized from this population in the SCS and source tables were provided in the submission. It should be noted that there is a significant overlap across the study populations. For example, within the 325 patients in the overall safety population, 257 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. This PPP population is now part of the ISS2.

There were two ongoing studies with 160 mg mobocertinib QD in treatment-naïve patients, TAK-788-1003 Part 2 (in Japanese patients, n = 33) and TAK-788-3001 (n = 140), that were not included in the first integrated safety analysis (ISS1, subject of the not updated SCS). Therefore, the applicant was asked to present and discuss the reported AEs, AESIs and SAEs from these studies.

Studies included in the updated ISS as of November 2021 (ISS2)

The updated ISS as of November 2021 (ISS2) continues not to include patients treated in ongoing RCT TAK-788-3001 with the argument that this trial is still blinded to the sponsor/applicant.

The ISS2 comprises now, however, safety data from treatment naïve patients in part 2 of trial TAK-788-1003 expanding both the overall and the 160 mg QD populations by 33 (Japanese, treatment naïve) patients.

The former "101 part 3" is no longer an own safety population of ISS2 but has been, in effect, replaced by a pretreated safety subpopulation.

A prior platinum safety subpopulation was not part of ISS1 but is discussed in the (not updated) SCS. This is now a prespecified sub-population of ISS2.

An entirely new safety analysis subset of ISS2 is the treatment-naïve population.

Thus, subject of ISS2 are 2 (open, non-controlled) studies (101 part 1, 2, and 3 as well as 1003 part 1 and 2) discerning prospectively overall 5 safety populations:

- Overall Safety (n = 358)
- 160 mg QD (n = 290)
- Pretreated (n = 226)
- Pooled Prior Platinum (n = 114)
- Treatment Naïve (n = 64)

Demographic and baseline characteristics

Median age of patients in the different analysis populations is 59 – 61 years {updated: 60-63.5 years}, with 65 – 67 % of participants being female {updated 65%-67}. While other demographic characteristics are comparable between the analysis populations in the ISS1, there is a majority of patients designated as "Asians" in 101-3 (69 %, white: 29 %) compared to the 160 mg QD (population /safety set) (40 %, white: 54 %) and overall analysis populations (37 %, white: 56 %).

In the updated ISS (cutoff Nov 2021), there is a majority of patients designated as "Asians" in the Pooled Prior Platinum (60 %) and Treatment Naïve populations (61 %). In the 160 mg QD population there are 47 % Asians and 48 % White. The overall numbers are Asians: 42 %, White 51 %, and Black/African American: 4 %.

Medical conditions at baseline were discussed by the applicant in the response and are overall comparable between the analysis populations.

Patient exposure

The overall median time on treatment in the patient populations in ISS1 were 5.29 (overall), 6.05 (160 mg QD) and 6.80 months (Study 101-3).

For the 5 populations of the ISS2 the corresponding median values were 5.88 (pretreated), 7.38 (pooled prior platinum), 7.56 (treatment naïve), 6.49 (160 mg QD) and 5.50 (overall) months.

For the 160 mg QD population, 90 % of patients are treated ≥ 1 month, 72 % {73%} are treated ≥ 3 months, but only 50 % {52%}, are treated for ≥ 6 months and 25% for ≥1 year {26%}). Consequently, for AEs with time-to-onset > 6 months, conclusions must be drawn cautiously.

Mean dose intensity is 134 mg/day {133 mg/day} for the 160 mg QD population and 142 mg/day for the Study 101 Part 3 population {not reported in ISS2, 136 mg/day for the pretreated population as of

ISS2). Thus, dose intensity is considered acceptably close to the suggested 160 mg QD starting dose in this application.

Adverse events

The most common treatment-emergent AEs (TEAEs) /related AEs (TRAEs) were from gastrointestinal (GI) disorders system organ class (SOC) (numbers from initial and updated (u) 160 mg QD: 98 %/95 %, u: 98 %/96 %), the most frequent preferred terms (PT) being diarrhoea (93 %/91 %, u: 94 %/93 %), nausea (47 %/40 %, u: 49 %/42 %), vomiting (37 %/28 %, u: 37 %/28 %) and stomatitis (29 %/27 %, u: 33 %/31 %). Decreased appetite was reported in 35 %/27 % (u: 37 %/28 %). Skin and subcutaneous tissue disorders was the second most common SOC (84 %/82 %, u: 86 %/84 %), with rash (38 %/37 %, u: 39 %/38 %) and dry skin (30 %/28 %, u: 31 %/29 %) as the most frequently reported PTs. Paronychia was common (28 %/28 %, u: 33 %/32 %), as was increases in hepatic enzymes (AST: 14 %/9 %, u: 14 %/10 %, ALT: 11 %/8 %, u: 12 %/9 %), pancreatic enzymes (amylase: 20 %/16 %, u: 22 %/18 %, lipase: 16 %/14 %, u: 20 %/17 %) and blood creatinine (29 %/18 %, u: 30 %/20 %). Anaemia was reported in 30 %/16 % (u: 29 %/17 %), and, of note, ECG QT prolonged (8 %/7 %, u: 12 %/11 %).

Frequencies from the updated 160 mg QD analysis population are in line with data presented in the original submission, but tend to be higher, particularly for QTc interval prolongation.

The overall incidences of AEs are comparable between the three safety populations presented in the initial submission, and are comparable between the five analysis populations presented in the response. Additionally, AEs are mainly in line with previously described AEs related to other EGFR-TKIs.

The most common grade ≥3 AEs (160 mg QD) were (initial/updated): diarrhoea (20 %/21 %), anaemia (7 %/ 6 %), hypertension (7 %/ 7 %), pneumonia (4 %/5 %), ECG QT prolonged (2 % /5 %), dyspnoea (5 %/ 4 %), lipase increased (4 %/ 5 %), lymphocyte count decreased (3 %/4 %), and stomatitis (4 %/3 %). The incidences of higher grade TEAEs are comparable in the different analysis populations.

Dose modifications and discontinuation due to AEs

Dose modifications are common (160 mg QD population: 68 %, u 72 %). Within the safety populations, AEs were most often managed by dose interruption (160 mg QD; 61 %, u: 66 %). Diarrhoea was the most common cause of drug interruption (160 mg QD: 25 %, u: 26 %), followed by nausea (160 mg QD: 12 %, u: 13 %) and vomiting (160 mg QD: 9 %, u: 8 %). Across the safety populations, 22 – 32 % (u: 27 – 55 %) required a dose reduction due to an AE, with diarrhoea as the single most common cause (9 – 14 %). Despite widespread dose interruptions, mean dose intensity is still 122 mg (overall population) – 134 mg (160 mg QD population) and 142 mg (Study 101 Part 3), which may indicate that interruptions are brief.

AEs leading to dose discontinuation occurred in 10 % (101-3, not presented in the updated ISS), 19 % (160 mg QD, updated: 18 %) and 21 % (overall, updated: 20 %), with GI disorders (4 % - 8 %) and respiratory-related AEs (overall: dyspnoea 2 %, pneumonitis 2 %) being the most common causes. In the response, data show that AEs leading to dose modifications are more common in the treatment-naïve group (81 %), with 55 % requiring a dose reduction. This analysis population was not presented in the original submission.

Serious adverse events and deaths

Treatment-emergent SAE occurred in approx. half of mobocertinib-treated patients, and data from the original submission are consistent with the updated analysis based on the latest data-cutoff. Initial/updated (u) numbers from160 mg QD: 46 %/47 % and overall: 47 %/48 %. The most common

SAE were reported with comparable frequencies across all analysis populations, with dyspnoea (5-6 %, u: 3-7 %), diarrhoea (5 %, u: 3-8 %), vomiting (4-5 %, u: 3-6 %) and pneumonia (1-5 %, u: 2-5 %) being the most prevalent. Treatment-related SAE were reported in 16-18 % (u: 16-20 %), most commonly diarrhoea (4 %, u: 3-6 %), vomiting (3-4 %, u: 3-4 %), dehydration (2 %, u: 1-3 %) and acute kidney injury (2 %, u: 1-3 %).

Overall, updated data show that there are 49 reported on-study deaths. This is 14 % of the overall safety population, in line with the 13 % reported previously. According to the applicant, 3 (overall) of the 41 (u: 49) on-study were drug-related; one case each of cardiac failure, respiratory failure and pneumonitis, respectively. Most patients included in the studies have stage IV NSCLC irresponsive to treatment. In addition, several patients present with severe comorbidities. It is therefore expected that most deaths during the study period are related to NSCLC or other diseases.

Adverse events of special interests (AESI)

The applicant has identified the following as AESIs: "Pneumonitis/ILD", "Cardiac disorders", "GI toxicities", "Stomatitis", "Skin-related events", and "Amylase/lipase increase", which are all relevant. Paronychia is a common AE associated with EGFR-inhibitors. This could have been included as a separate AESI, but is rather covered by the term "Skin-related events".

Eye disorders is an identified risk associated with several EGFR-TKIs, indicating a class effect, that was not discussed in the original application and was thus requested. In the response, adding information on ocular toxicity to the product information was suggested, thereby reflecting this risk sufficiently

AESI: GI toxicities (diarrhea, nausea, vomiting)

Relevant aspects have already been discussed in previous paragraphs. Gastrointestinal toxicity is very common for mobocertinib and all EGFR-TKIs. This is mostly lower grade and manageable.

AESI: Pneumonitis/ILD

Pneumonitis/ILD is a known class-effect of EGFR-TKIs and was reported in 2-4 % overall population (u: 2-8 %) and in 3% (u:4%), in 160 mg QD population treated with mobocertinib. One mobocertinib-related death caused by pneumonitis was reported at 120 mg. Compared to other EGFR-TKIs, dacomitinib (0.5 %) and afatinib (1.6 %), the frequency of ILD is higher with mobocertinib, but is more comparable to osimertinib (3.7 %), . While this constitutes an important safety issue for mobocertinib, , the information included in the SmPC is considered to reflect this risk appropriately.

AESI: Cardiac disorders (including QTc interval prolongation)

In the original submission between 33-39 % of patients reported PTs in this SOC, most events were classified as lower grade 1 or 2 (86-87 %), non-serious (89-90 %) and not related to treatment (84-89 %). Of serious events, cases of cardiac failure (n = 2), cardiac failure congestive (n = 1), cardiomyopathy (n = 1), and ejection fraction decreased (n = 2) were reported. There was one fatal event of cardiac failure, which occurred in a patient with a history of cardiovascular complications including cardiac failure that was worsened by mobocertinib. Of the EGFR TKIs indicated for NSCLC (afatinib, dacomitinib, osimertinib and erlotinib) only osimertinib include a warning on cardiac toxicity to which mobocertinib appears comparable.

Median TTO for cardiac disorders was 79 to 82 days and time to resolution was approximately 2 weeks. From ISS1 a case of cardiac failure congestive had TTO of 210 days, and a case of cardiomyopathy had TTO of 645 days. Even if most AEs in this class debut early, serious events may manifest late. Long-term safety data for mobocertinib is still very limited, with only 84 patients exposed for $\geq$ 12 months as of the latest cut-off (12 additional patients compared to the initial submission). This imposes an uncertainty to the estimated incidences.

ECG data collected in Study 101 demonstrated a moderate QT prolonging effect for mobocertinib (15-20 ms) at doses of 120 mg daily and above, and the extent of QTc-prolongation in mobocertinib-treated patients was unexpected in light of non-clinical studies. Based on data from the first cutoff, QTc interval prolongation was reported in 10 % in 101-3, 8 % in 160 mg QD, and 7 % in the overall safety population. One case of Torsade de Pointes, which was deemed related to treatment, was reported. The incidences have increased following the latest cut-off, and QTc prolongation is now reported for between 11 % (overall) to 18 % (pooled prior platinum) of patients, with 12 % of patients in the 160 mg QD experiencing an event, which is a 50 % increase.

The ADR table in the SmPC has been updated with the new and higher frequencies of QTc prolongation (12 %, grade 3: 4.5 %, grade 4: 0.3 %) and cardiac failure (3.4 %, grade 3: 1.0 %, grade 4: 0.3 %). Further information is added to 4.8 and 4.4, including information that life-treathening and fatal cases have been reported. Of note, although TEAE tends to be higher in non-Asians, analysis of genetic ancestry revealed more frequent and severe QTc prolongation in the Asian patient sub-group, and is addressed in sec. 4.8 of the SmPC.The cardiac toxicity profile of mobocertinib is of particular concern and appears to be more severe than for other TKIs in the class, which is worrisome. However, it is considered that the severity of these adverse events is adequately described ..Further, as requested in the D120 LoQ, conducting cardiac monitoring and periodic ECG monitoring is now advised for all patients, and not just for patients with risk factors as was previously described.

AESI: Stomatitis

Stomatitis (including mouth ulceration, aphthous ulcer, mucosal inflammation, cheilitis, angular cheilitis, and odynophagia) is a known risk for EGFR-TKIs and was commonly reported for mobocertinib (related events: 160 mg QD: 33 %, updated number (u): 36 %, overall: 29 %, u: 32%). Reassuringly, the reported events were not serious and were overall manageable with standard care TTO is short (8-9 days), but resolvement is slow (approx. 5 – 7.5 weeks). The risk is considered to be adequately addressed in the product information.

AESI: Skin-related events

EGFR TKIs are known to cause a variety of skin-related events, which is also described for mobocertinib. Related events (initial data/updated data) were reported in 84 %/86 % in the 160 mg QD and 77 %/80 % overall, with rash (32-45 %/34-46 %) and dry skin (26 -31 %/27-31 %) as the most commonly reported PTs. This drug class is associated with a high prevalence of paronychia, which is reported in 25-40 %/28-44% of mobocertinib-treated patients.

SJS/TEN has been reported for gefitinib, erlotinib, afatinib and osimertinib, indicating that this is a class effect of EGFR-TKIs, which the applicant was requested to discuss in the response. As of the latest data cutoff, no cases of SJS/TEN have yet been reported for mobocertinib, which is reassuring. As these are rare events, post-marketing surveillance of SJS/TEN will be important. Consequently, data are insufficient to conclude if mobocertinib has a better skin toxicity than other EGFR-TKIs, but based on current knowledge, the risk is now acceptably addressed in the product information.

AESI: Amylase/lipase increase

An increase in amylase and/or lipase was reported in 20 %/15 % (updated: 16 %/16 %) of patients in the overall safety population, with few higher-grade cases. Median TTO is short (1-2 weeks), with recovery within 2-3.6 weeks. Pancreatitis has been reported for other EGFR-TKIs, but not for mobocertinib Amylase and lipase increased is included as ADRs in the SmPC, and this risk is thus sufficiently addressed.

Laboratory

Apart from anaemia, which was proposed as an ADR with very common frequency, the original application included no discussion on changes in hematologic values. From tables/figures in the ISS (first cutoff) , there were reports of drug-related thrombocytopenia (4 %), leukopenia (2 %) and neutropenia (2 %) (160 mg QD). Decreases in the levels of lymphocytes, leukocytes, neutrophils and platelets (in addition to haemoglobin) were described during the first cycles of mobocertinib treatment.

The applicant was therefore asked to provide an overview over shifts in blood cell levels/hematologic parameters during treatment, discuss relation to treatment and the need to update the SmPC. Due to the high frequency of reported shifts (updated data in the 160 mg QD group): haemoglobin (65%), lymphocyte count (53%), platelet count (29%), and white blood cell count (24%), including higher-grade shifts, this information has been added as ADRs in the response.

Increases in transaminases and bilirubin are reported for several EGFR-TKIs, some of which include warnings on hepatotoxicity in SmPC 4.4 (such as dacomitinib and gefitinib). Increases in hepatic enzyme parameters were commonly reported with mobocertinib (initial/updated numbers in 160 mg QD, AST increased: 23 %/ 25 %, ALT increased 24 %/25 %), as are grade ≥3 shifts (updated data in 160 mg QD: AST 2 %, ALT 3 %). As of the latest cutoff date, no case of severe liver toxicity has been described in the mobocertinib clinical program. The high prevalence of increased liver enzymes raised a concern, and the applicant was asked to discuss whether additional information in the SmPC (warning in 4.4. and advice on monitoring) could be useful. Following the response to this question, the applicant has added a section on liver enzymes to the SmPC 4.8. With minor revisions, this is considered to address this concern appropriately (subject to SmPC OC).

Electrolyte disturbances are common in mobocertinib-treated patients and may be of higher grade, which was seen in the original submission and led to an OC. In the response, the applicant discussed consequences of electrolyte imbalance, with shifts/grade ≥3 shifts of hypokalaemia (160 mg QD updated: 28%/5%), hyponatraemia (26%/5%), and hypomagnesaemia (30%/2%) as ADRs in the SmPC. Further, dehydration and AKIs has also been added as ADRs. The risk is now appropriately reflected in the SmPC.

Safety in special populations

The applicant was asked to discuss more thoroughly differences in reported AEs between patient groups of different age, biological sex and genetic ancestry.

The applicant has updated (and discussed) the data for the 160 mg QD population (290 patients, 176 patients below the age of 65, 114 patients 65 years of age or older). Although the numbers are slightly different, the information is in essence the same: Grade ≥ 3 and serious AEs were more frequent for the older patients (80% vs. 65% and 54% vs. 42%) mainly due to more frequent grade > 3 diarrhea (26% vs. 17%). The latter is addressed in the updated SmPC.

The applicant has updated the data for the 160 mg QD population (290 patients, 100 male patients, 190 female patients). In essence, the (updated) conclusion of the applicant, while there were some differences in TEAEs between male and female patients, Grade ≥3 TEAEs and SAEs by individual PTs were generally similar, and that no clinically significant differences were identified, is valid also for the CHMP.

The applicant has also updated (and discussed) the data for the 160 mg QD population having becoming larger by 33 patients with Japanese ancestry (now 290 patientsoverall; 135 Asian patients, 152 non-Asian patients; 3 gentic ancestry not reported). The proposal of the applicant to implement the updated analysis as to gentetic ancestry in sec. 4.8, for the description of selected adverse reactions (QTc Interval Prolongation, Diarrhoea) is adequate.

3.3.9. Conclusions on clinical safety

With reference to the limitations of the small safety data pool submitted, the assessment of the analysis presented indicate that mobocertinib has an acceptable safety profile.

Of specific concern is that mobocertinib appears to be associated with a high risk of cardiac toxicity/heart failure (including a fatal case), a high occurrence of QTc prolongations (including a case of Torsade de pointes), and pneumonitis/ILD (including a fatal case).

Overall, the AEs noted with mobocertinib were consistent with the anticipated mechanism and described safety profile of the class of EGFR TKIs. Most adverse events appear to be manageable with standard care and dose modifications. However, the majority of TEAEs do not resolve after dose modification (interruption of application and/or dose reduction). Results over time, including discontinuation due to AE frequencies, indicate that prolonged treatment with mobocertinib has acceptable tolerability.

3.4. The application is approvable from a safety point of view, provided that the OCs in the LoOI are addressed.Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant identified the following safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	• Pneumonitis/Interstitial Lung Disease • Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation • Cardiac failure
Important potential risks	• Reproductive and developmental toxicity
Missing information	• Use in patients with severe renal impairment • Use in patients with moderate or severe hepatic impairment • Long-term use

1.1.1.1 Discussion of the safety specification

The applicant provided an updated list of important risks and missing information in version 0.3 of the RMP. Based on the question raised in the Day 120 LoQ, the applicant renamed the important identified risk "QTc interval prolongation" to "Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation".
Furthermore, the Missing information "Drug-drug interactions with substrates of CYP3A" was removed from the list of safety concerns based on completion of CSR for study TAK-788-1004. Concerning this issue, the applicant states:
"Mobocertinib is metabolized predominantly by CYP3A. Therefore, moderate or strong CYP3A inhibitors or inducers were excluded during clinical development due to their potential effect on systemic exposures

of mobocertinib. Drug-drug interaction studies and PBPK analyses have subsequently been performed to assess the effect of moderate or strong CYP3A inhibitors or inducers on the PK of mobocertinib.
Drug-drug interaction studies and PBPK analyses demonstrated that the coadministration of mobocertinib with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations. Increased mobocertinib plasma concentrations may increase the risk of AEs. Similarly, available data indicate that the coadministration of mobocertinib with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations, which may decrease the efficacy of mobocertinib. The proposed prescribing information includes dosing recommendations to mitigate the risk of potential drug-drug interactions. Consequently, "Drug-drug interactions with substrates of CYP3A" can be removed as missing information.
In conclusion, the list of safety concerns is alignment with the point raised above.

1.1.1.2 Conclusions on the safety specification

The safety specifications are acceptable.

3.4.2. Pharmacovigilance plan

On-going and planned additional pharmacovigilance activities are summarized in below table.

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 – Required additional pharmacovigilance activities				
Study TAK-788-3001 Status: Ongoing	To assess the safety and tolerability of TAK-788 in comparison with platinum-based chemotherapy as first-line treatment in patients with non–small cell lung cancer With EGFR Exon 20 insertion mutations.	Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation; Cardiac failure; Pneumonitis/Interstitial Lung Disease; and Long-term use	Study Completion Final report submission	September 2023 March 2024

Routine pharmacovigilance activities for the important potential risk "reproductive and developmental toxicity" are considered sufficient, as the risk is sufficiently described in the SmPC and expected for a cancer therapy.

The important identified risks "Pneumonitis/Interstitial Lung Disease", "Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation " and "Cardiac failure" have occurred in the clinical trial programme.

In order to gain more information about these important identified risks, the applicant included study TAK-788-3001 in Part III of the RMP.

Title of the study: A Randomized Phase 3 Multicenter Open-label Study to Compare the Efficacy of TAK-788 as First-line Treatment Versus Platinum-Based Chemotherapy in Patients With Non–Small Cell Lung Cancer With *EGFR* Exon 20 Insertion Mutations.
159 subjects are planned for each of two treatment groups.
Referring to the amended protocol (no. 6, dated 22 Jan 2021), this study is mainly an efficacy study to compare the efficacy of TAK-788 vs platinum-based therapy with progression-free survival as primary endpoint.

One of the secondary objectives is as follows:
"To compare patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module, QLQ-LC13, in patients treated with TAK-788 compared with those treated with platinum-based chemotherapy."
In addition, ECG and echocardiogram/MUGA scans will be collected.

These measures will help identify and cover the important identified risks "Pneumonitis/Interstitial Lung Disease", "ventricular arrhythmias" and "Cardiac failure".
The reported rates of the AEs of clinical interest of pneumonitis/ILD were 2%-4%. The most common event was pneumonitis (1% to 3% of patients). QT prolongation was reported from 7-10% of the patients.
159 patients in the TAK-788 arm of a clinical trial would only show few patients with ILD or QT prolongation.

Therefore neither the study objectives nor the number of patients are considered sufficient to fully characterise the risks and potential new safety issues.

The applicant is requested to propose a registry/registry study in order to cover "Pneumonitis/Interstitial Lung Disease" and "QTc interval prolongation", "Cardiac failure" and "long-term safety".

Nevertheless, the applicant should provide safety information from study TAK-788-3001 in the PSURs.

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product and the applicant should propose PhV studies.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.3. Risk minimisation measures

Summary of risk minimisation measures of the RMP are summarized in below table.

Safety concern	**Routine risk minimisation activities**	
Pneumonitis/Interstitial Lung Disease	**Routine risk communication:** Summary of Product Characteristics (SmPC) section 4.2; section 4.4; and section 4.8. Package leaflet (PL) section 2; section 4	

	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommended dose modifications in case of pneumonitis/ILD are included in SmPC Section 4.2. The prescribers are advised to recognise early the patient's sign / symptoms of pneumonitis/ILD. The prompt intervention, conservative management and drug discontinuations approach as recommended in SmPC section 4.4. Patients/Caregivers are informed of sign/symptoms of pneumonitis/ILD and advised to contact to HCPs immediately in case of sign/symptoms observed. **Other routine risk minimisation measures beyond the Product Information:** None.
Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation	**Routine risk communication:** SmPC section 4.2; section 4.4; section 4.8 and section 5.1. PL section 2; section 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The prescribers are advised to routinely monitor patients for QTc interval prolongation and electrolytes and to follow recommendations on dose modifications (including dose reduction / drug interruption or discontinuation) as included in SmPC section 4.2 and 4.4. Patients/Caregivers are informed of sign/symptoms and advised to contact to HCPs immediately if observed. **Other routine risk minimisation measures beyond the Product Information:** None.
Cardiac failure	**Routine risk communication:** SmPC section 4.2; section 4.4 and section 4.8. PL section 2; section 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The prescribers are recommended to conduct periodic monitoring of cardiac parameters, including assessment of left ventricular ejection fraction at baseline and during treatment, in patients with cardiac risk factors. The close conservative management along with dose modifications (including reduction, interruption and drug discontinuation) approach is recommended in SmPC section 4.2 and 4.4. Patients/Caregivers are informed of sign/symptoms and advised to contact to HCPs immediately if observed. **Other routine risk minimisation measures beyond the Product Information:** None.
Reproductive and developmental toxicity	**Routine risk communication:** SmPC section 4.4 and section 4.6. PL section 2. **Routine risk minimisation activities recommending specific clinical**

	measures to address the risk: The prescribers are informed to emphasise the patients on need of adequate contraception, and potential hazards to the foetus in case of mobocertinib exposure during pregnancy, as mentioned in SmPC section 4.4 and 4.6. The patients are advised to discuss on the use of the effective method of contraception during and after stopping mobocertinib therapy with treating physicians. **Other routine risk minimisation measures beyond the Product Information:** None.
Use in patients with severe renal impairment	**Routine risk communication:** SmPC section 4.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None.
Use in patients with moderate or severe hepatic impairment	**Routine risk communication:** SmPC section 4.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None.
Long-term use	**Routine risk communication:** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None.

SmPC = Summary of Product Characteristics; ILD = Interstitial Lung Disease.

The routine risk minimisation measures have been adequately described and are acceptable.

Overall, the PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

3.4.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.0.3 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

The applicant/Proposed Future MAH has submitted a signed Summary of the applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS/Rapporteur considers the Summary acceptable.

3.5.2. Periodic Safety Update Reports submission requirements

A PSUR cycle of 6 months is required.

4. Benefit risk assessment

Exkivity (mobocertinib) is an orally available kinase inhibitor of the EGFR that irreversibly binds to EGFR exon 20 insertion mutations at lower concentrations than Wild type (WT)-EGFR leading to the inhibition of the receptor activity.

4.1. Therapeutic Context

4.1.1. Disease or condition

The initially claimed indication in this MAA for Exkivity (mobocertinib) was:

> "*Exkivity as monotherapy is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received prior platinum-based chemotherapy*"

The claimed indication was changed during the procedure to:

> "*Exkivity as monotherapy is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive advanced non-small cell lung cancer (NSCLC), who have received prior platinum-based therapy*".

Locally advanced and metastatic NSCLC is a progressive, deadly disease. In this disease setting, the aim of treatment is to prolong overall-survival, and/or to improve symptoms, whilst minimising toxicity.

The most common oncogenic driver mutations in NSCLC are activating mutations in the epidermal growth factor receptor (EGFR), and multiple approved tyrosine kinase inhibitor (TKI) drugs are targeted against these molecular aberrations. The present application concerns a subset of patients with EGFR Exon 20 insertion mutations, who constitute 4-12% of patients with an activating EGFR mutation that account for ~2% of all NSCLC patients.

Details of the definition of a positive EGFR exon 20 insertion mutation status used in the pivotal study of this MAA lack clarification.

4.1.2. Available therapies and unmet medical need

With the exception of those patients found to have low frequency insertion mutations, such as A763_Y764insFQEA, most patients with NSCLC harbouring EGFR exon 20 insertion mutations (~95%) are usually resistant to first and second-generation EGFR TKIs erlotinib, gefitinib, afatinib, or dacomitinib (NCCN guideline, NSCLC, Version 6.2021). The third generation EGFR TKI osimertinib has also been evaluated in a small single-arm trial in patients with NSCLC with EGFR exon 20 insertion mutations, and showed some interesting activity [Veggel et al 2020, Piotrowska et al 2020].

However, patients with metastatic NSCLC (adenocarcinoma) harbouring EGFR exon 20 insertion mutations are usually treated as patients without a driver mutation. Initial treatment usually consists of carboplatin or cisplatin in combination with pemetrexed with or without an immune checkpoint (PD-1/PD-L1) inhibitor. Subsequent therapy options include systemic immune checkpoint inhibitor monotherapy (if no previous IO) or (independent of previous IO) monotherapy with docetaxel, pemetrexed, gemcitabine or combination therapy with ramucirumab/docetaxel (NCCN 6.2021 - NSCLC).

Lately, Amivantamab and mobocertinib received accelerated approval in the USA for the patient population discussed in this MAA in May and September 2021, respectively. In the EU Amivantamab received a CMA in December 2021. Its role in treatment is to be clarified.

While there is certainly an unmet need for better treatment options, treatment options are available in the EU. Therefore, mobocertinib needs to show the fulfilment of an unmet medical need / a major therapeutic advantage over these existing therapies in the context of CMA.

4.1.3. Main clinical study

The efficacy claims of mobocertinib in this MAA are based on the single pivotal study AP32788-15-101. Study AP32788-15-101 is an uncontrolled, open-label phase 1/2 first-in-human study with several protocol amendments changing key elements of the study design. Overall study population included is a typical broad oncological population of a first-in-human study. The study has a dose escalation phase (part 1) and a consecutive dose expansion phase (part 2) in different molecularly and histologically defined cohorts. Based on data from the dose escalation and dose expansion phase the applicant amended the study and added an extension phase (part 3) to the study, including patients with previously treated locally advanced or metastatic NSCLC whose tumours harbour EGFR exon 20 insertion mutations. This extension phase (part 3) was added with the aim to provide pivotal evidence in an MAA for the included population and was to be analysed when all patients had had the opportunity to be followed for 6 cycles, which resulted in a data cut-off date of 29 May 2020. However, as to the applicant, the FDA advised to include a pooled prior platinum analysis set as an additional analysis set. In addition, another data cut-off was added to give the majority of responding patients an opportunity to be followed for at least 6 months from the onset of response (01 November 2020). In the course of this marketing authorisation procedure another data cut-off for efficacy data was added (01 November 2021).

Recruitment started in June 2016 for part 1, in January 2018 for part 2 and in February 2019 for part 3. In June 2018 the applicant received CHMP scientific advice (EMEA/H/SA/3828/1/2018/III) not to perform the proposed uncontrolled extension cohort (at that point not yet started) with the aim to provide pivotal data as it was deemed "unlikely that data reported from the proposed uncontrolled extension cohort would be considered sufficient to support an approval". ORR ranges discussed in the advice were in the same range of the data presented in this current MAA.

To support this uncontrolled clinical study data, the applicant performed study TAK-788-5002, a non-interventional (observational) retrospective study using longitudinal data from the Flatiron Health

Research Database, a US-nationwide electronic health record (EHR)-derived database. The aim of this analysis of real-world data (RWD) on patients with NSCLC and EGFR exon 20 insertion mutations was contextualisation of the pivotal SAT by providing a historical benchmark as supportive information. In addition to the RWD study TAK-788-5002 using EHRs from the US, the applicant collaborated with academic investigators to conduct a retrospective chart review in Germany. Longitudinal data were collected and analysed from patients with NSCLC with EGFR and HER2 exon 20 insertion mutations from 12 academic thoracic oncology centres across Germany.

4.2. Favourable effects

Study AP32788-15-101 (pivotal study)

Primary endpoint:

Confirmed ORR (cORR) by independent review committee (IRC) was 26.0% (25/96 patients, 95% CI: 17.6, 36.0) and 28.1% (32/114 patients, 95% CI: 20.1, 37.3) in the pre-specified Part 3, full analysis set and the pooled prior platinum analysis set, respectively.

Sensitivity analysis of cORR by investigator-assessed tumour response (INV) showed ORR at 32.3% (95% CI: 23.1, 42.6) and 35.1% (95% CI: 26.4, 44.6) in the Part 3, full analysis set and the pooled prior platinum analysis set, respectively.

Secondary endpoints

Median duration of response (DoR) (by IRC) was 15.77 months (95% CI: 7.39, 19.35) in the pooled prior platinum analysis set.

Median OS was 20.17 months (95% CI: 14.88, 25.26) in the pooled prior platinum analysis set.

Median PFS was 7.29 (95% CI: 5.52, 9.23) in the pooled prior platinum analysis set.

TAK-788-5002 (supportive study; retrospective observational RWD study)

rwORR for the trial aligned patients was 11.1% and for the prior platinum trial-aligned patients 14%.

4.3. Uncertainties and limitations about favourable effects

Study AP32788-15-101 (pivotal study)

The efficacy claims of mobocertinib are based on a single pivotal uncontrolled open-label phase I/II study.

The exploratory nature of the study, with major protocol amendments based on study data and external data and lack of hypothesis testing, are major sources of uncertainty in the interpretation of the results.

Due to the non-randomised/single-arm open-label design, the risk of bias cannot be eliminated. The most challenging issue is the selection of patients for the trial and how the applicant can assure that an unselected patient population has been studied. Nevertheless, this is only the most obvious bias that may be present in a single arm clinical trial.

The indication applied for is based on a post-hoc defined subpopulation of the pivotal study ('pooled prior platinum analysis set'). Of note, in the pre-specified pivotal study population (part 3 full analysis set, extension phase) primary endpoint cORR (IRC) was 26% (95% CI: 17.6, 36.0), i.e. 2% lower than in the post-hoc defined 'pooled prior platinum analysis set'.

The clinical relevance of ORR (as primary efficacy endpoint) for NSCLC patients is unclear.

The study population included into extension cohort part 3 is predominantly Asian (68.8%), female (64.6%), below 65 years of age (63.5%) (median and mean age 59 years), never smokers (72.9%), 2nd-line (51%), has an ECOG status 0 or 1 (100%) and has an adenocarcinoma (99.0%) (the population of the 'pooled prior platinum analysis set' is comparable). A better survival prognosis including better response rates can be assumed for this study population in comparison to the European standard NSCLC Stage IV population. This expectation is in line with the subgroup analyses provided for the 'pooled prior platinum analysis set', showing better response rates for the above mentioned subgroups, where available.

Duration of Response (DoR) only applies to the subpopulation of responding patients. Due to the low cORR reported, the value of this endpoint is weak as it describes only a small subpopulation in this study. In consequence the confidence interval reported is very broad.

For time to event endpoints such as OS and PFS, no isolation of drug effects is possible, as they reflect to a high degree also the tumour biology, the inherent prognosis of the disease, the patients' performance status and comorbidities (list incomplete). No efficacy claims can be based on PFS and OS data from the pivotal study provided.

TAK-788-5002 (supportive study; retrospective observational RWD study)

Meaningful context can only be provided if patients from the relevant analysis sets from the pivotal SAT and RWD study are comparable with regard to baseline factors influencing prognosis. Therefore, only analyses based on study-aligned patients may provide context. However, while including only patients aligned with key eligibility criteria of pivotal study part 3 and prior platinum analysis set is a necessary requirement to achieve alignment, it is not sufficient to ensure matching of analysis populations with regard to prognostic factors. Indeed, differences were noted regarding some baseline characteristics, and additional baseline differences may be possible for additional factors where no information was available or which are yet unknown. A major difference is also that Flatiron data are US-based, while the majority of patients in the pivotal study part 3 were recruited in Asia (60%) and only 30% in North America

Although the attempts for standardization and providing a high data quality are acknowledged, the endpoints must still rely on the information available in electronic health records (EHRs) such that data quality is basically dependent on the data quality in the underlying EHRs that is not under control of the sponsor. Consequently, response or progression endpoints based on EHR where data are not collected in a systematic and standardized way cannot be considered as comparable to the corresponding endpoints based on systematic data collection within an interventional clinical trial. Even collection of mortality data from RWD is more challenging such that even analysis of OS may be susceptible to bias because of missing data.

Generally, the relatively large proportion of patients in the analysis sets without tumour assessments (~ 25%) raises the concern that these data may not be an adequate source for a reliable evaluation of response to provide an adequate historical benchmark. It is acknowledged that excluding patients without tumour assessments from the analysis may lead to selection bias, particularly when it could be assumed that not performing tumour assessments is associated with a lower likelihood of response (e.g. if no tumour assessment is performed because of deteriorating disease). Otherwise, generally handling missing data as non-response in the analysis (i.e. assuming that all patients without tumour assessments are non-responders) probably leads to an underestimation of response, which may lead to an inappropriately low RWD benchmark, particularly considering the large proportion of patients without tumour assessments.

Although the Flatiron database covers 2.4 million US active cancer patients, only 63 patients were included in the trial-aligned cohort and 50 patients in the prior platinum-aligned cohort. Due to these small patient numbers, precise estimates cannot be provided based on this study.

Differences between trial-aligned patients and patients from pivotal study part 3 regarding baseline demographic factors (age, race) and baseline clinical characteristics (stage, prior therapy lines) are noted.

Almost 25% of trial-aligned patients (15/63) and prior platinum-trial aligned patients (12/50) had no tumour assessments, which raises general concerns whether these data are an adequate source for a reliable evaluation of response. Patients without tumour assessment were considered as non-responders in the analysis. Obviously, this implies that in patients with tumour assessments, response rates were larger (14.6% instead of 11.1% for trial-aligned patients; 18.4% instead of 14% for prior platinum trial-aligned patients).

D-E-R

Dose-response, and exposure-response for efficacy is to a large extent undescribed.

4.4. Unfavourable effects

Studies performed to support the safety profile of 160 mg mobocertinib QD for NSCLC are the closed and uncontrolled AP32788-15-101 (part 1/2/3 – "Study 101") and TAK-788-1003 (DLP November 2021). The safety analysis populations presented are "Pretreated" (n = 226), "Pooled Prior Platinum" (n = 114), "Treatment-Naïve" (n = 64), the "160 mg QD" population (n = 290, patients who have received at least one dose of 160 mg mobocertinib) and the "overall" safety population (n = 325, patients who have received any dose of mobocertinib). Safety data reflected in the SmPC are based on the "160 mg QD population". The median times on treatment are 5.50 (overall) and 6.49 months (160 mg QD). Mean/median daily dose intensities are: 133 mg/148mg (160 mg QD) and 122 mg/125 mg (overall).

Adverse events

The most common treatment-emergent AEs/related AEs were gastrointestinal (GI) disorders (numbers from the 160 mg QD population: 98 %/96 %), the most frequent preferred terms (PT) being diarrhoea (94 %/93 %), nausea (49 %/42 %), vomiting (37 %/28 %) and stomatitis (33 %/31 %). Decreased appetite was reported in 37 %/28 %. Skin and subcutaneous tissue disorders was the second most common system organ class (SOC: 86 %/84 %), with rash (39 %/38 %) and dry skin (31 %/29 %) as the most frequently reported PTs. Paronychia was common (33 %/32 %), as was increases in hepatic enzymes (AST: 14 %/10 %, ALT: 12 %/9 %), pancreatic enzymes (amylase: 22 %/18 %, lipase: 20 %/17 %) and blood creatinine (30 %/20 %). Anaemia was reported in 29 %/17 %, and, of note, QTc interval prolongation (12 %/11 %).

The most common grade ≥3 AEs (160 mg QD) were: diarrhoea (21 %), anaemia (6 %), hypertension (7 %), pneumonia (5 %), QTc prolongation (5 %), lipase increased (5 %), dysponea, amylase increased and lymphocyte count decreased (4% each).

Serious adverse events and deaths

Treatment-emergent SAE occurred in approx. half of mobocertinib-treated patients (160 mg QD: 47 %, overall: 48 %). Treatment-related SAEs in the 160 mg QD population/overall (17%/16%) was reported in 16-20 %, most commonly seen in the 160 mg QD were diarrhoea (4 %), vomiting (3 %), dehydration (2 %) and acute kidney injury (2 %).

Overall, there were 49 reported on-study deaths (12 % of the overall safety population); 3 of these were considered drug-related: one case each of cardiac failure, respiratory failure and pneumonitis, respectively.

Dose modifications and discontinuation due to AEs

Dose modifications are prevalent (overall: 72 %, 160 mg QD: 72 %), particularly drug interruptions (overall: 65 %, 160 mg QD: 66 %). Dose reductions were required in 32 % of patients overall (160 mg QD: 36 %). Diarrhoea and nausea/vomiting were the most common cases of dose modifications. AEs leading to dose discontinuation occurred in 18 % (160 mg QD) and 20 % (overall), with GI disorders (160 mg QD: 5 %) and respiratory-related AEs (160 mg QD: total 4 %, including pneumonitis 2 %) being the most prevalent causes.

Adverse events of special interest (AESI)

The following AESIs were identified: "Pneumonitis/ILD", "Cardiac disorders", "GI toxicities", "Stomatitis", "Skin-related events", and "Amylase/lipase increase",

"Gastrointestinal toxicity" and "Stomatitis" are very common for mobocertinib and all EGFR-TKIs. This is mostly lower grade and manageable. Regarding "amylase/lipase increase", there were few higher-grade cases. Pancreatitis has been reported for other EGFR-TKIs.

Pneumonitis/ILD

Pneumonitis/ILD is a known class-effect of EGFR-TKIs and was reported in 4 % of patients treated with mobocertinib (both overall and 160 mg QD). One mobocertinib-related death caused by pneumonitis was reported. Compared to other TKIs dacomitinib (0.5 %) and afatinib (1.6 %), the frequency of ILD is higher with mobocertinib (up to 4 %), but comparable to osimertinib (3.7 %).

Cardiac disorders and QTc interval prolongation

In the 160 mg QD37 (overall 36 %) % of patients reported PTs in this SOC, most events were classified as lower grade (85 %), non-serious (90 %) and not related to treatment (84%). There was one fatal event of worsening of existing cardiac failure. The concentration-QTc analysis indicated a concentration dependent increase in the QTc interval. QTc interval prolongation is reported in 12 % in 160 mg, and 11 % in the overall safety population. Of the EGFR TKIs indicated for NSCLC (afatinib, dacomitinib, osimertinib and erlotinib) only osimertinib include, as mobocertinib, a warning on cardiac toxicity.

Skin-related events

EGFR TKIs are known to cause a variety of skin-related events, which is also described for mobocertinib (related: 160 mg QD: 84 %, overall: 78 %).

4.5. Uncertainties and limitations about unfavourable effects

Main uncertainties and limitations about unfavourable effects derive directly from the small size of the safety population (290 patients in the '160 mg QD', and 358 patients in the overall population respectively) which limits any conclusion on infrequent AEs. Further limitations consist in the lack of randomised controls.

Study design and safety populations

In addition to the limited number of patients and uncontrolled design of the studies, the short median time of exposure (overall 5.5 months, 160 mg QD: 6.5 months) imposes further challenges on the interpretation of safety data. It must be highlighted that long-term safety data is strictly limited.

Cardiac toxicity and QTc interval prolongation

The serious cardiac events raise a concern. A case of cardiac failure congestive had TTO of 210 days, and a case of cardiomyopathy had TTO of 645 days. Even if most AEs in this class are lower-grade and debut early (within 80 days), serious events may manifest late.

QTc interval prolongation is reported in 10 % {12 %} in the 160 mg QD analysis set, and 11 % in the overall safety population. These numbers are considered high, and worringly the reported incidences have increased following the latest cut-off. It appears that mobocertinib is associated with a higher risk of cardiac toxicity/QTc prolongation than other EGFR TKIs. Cardiac monitoring and follow-up is considered important for all mobocertinib-treated patients, is now recommended in the product information addressing this uncertainty.

Pneumonitis/ILD

Pneumonitis/ILD is a class-effect of EGFR-TKIs. This constitutes an important safety issue including fatal events, which is addressed in the SmPC. However, ILD appears to be reported more frequently with mobocertinib than certain other EGFR-TKIs, but comparable to osimertinib. Pneumonitis/ILD is included as an important identified risk in the RMP.

D-E-R

Dose-response, and exposure-response for safety is to a large extent undescribed.

Pharmacokinetics

The impact of moderate to severe hepatic impairment and severe renal impairment on the pharmacokinetics of mobocertinib and metabolites (AP32960, AP32914) is not known. Until the results from the ongoing dedicated renal and hepatic studies 1007 and 1008 are available (PAM), current knowledge should be reflected in the SmPC (SmPC).

The DDI potential of mobocertinib and metabolites AP32960 and AP32914 was evaluated in clinical studies and by use of PBPK modeling, but is currently not considered sufficiently characterised. Current knowledge should be reflected in the SmPC (SmPC).

The impact of mobocertinib and active metabolites to the efficacy and safety profile is not clear due to issues raised concerning covalent binding to plasma proteins.

4.6. Effects Table

Effects Table for Exkivity (mobocertinib) in locally advanced or metastatic NSCLC patients with EGFR Exon 20 insertion mutation.

Effect	Short Description	Unit	Result	Uncertainties/ Strength of evidence/Comment
Favourable Effects	(study AP32788-15-101; 'pooled prior platinum analysis set', n = 114; data cut-off 01 Nov 2021)			
cORR (IRC)	confirmed objective response rate (includes patients with complete and partial response)	% (95% CI)	28.1 (20.1, 37.3)	post-hoc defined subpopulation of pivotal study One complete response reported (CR: n = 1/114)
DoR (IRC)	duration of response	months (95% CI)	15.77 (7.4, 19.4)	only applies to responding patients
PFS (IRC)	progression-free survival	months (95% CI)	7.29 (5.5, 9.2)	no isolation of drug effects is possible in SAT; therefore, no efficacy claim can be based on PFS number of patients with event 67%

Effect	Short Description	Unit	Result	Uncertainties/ Strength of evidence/Comment
OS	overall survival	months (95% CI)	20.17 (14.9, 25.3)	no isolation of drug effects is possible in SAT; therefore, no efficacy claim can be based on OS number of patients with event 58%

Effect	Short Description	Incidence	References
Unfavourable Effects	(160 mg QD population; 2nd ISS, n = 290; data cut-off Nov 2021)		
	In terms of TEAEs		
any TEAE	overall (on study)	**100%**	ISS
TEAE	drug related	**99%**	
grade ≥3 TEAE	severe	**71%**	
grade ≥3 TEAE (dr)	severe TE and drug related AE	**46%**	
TE SAE	serious TEAE	**47%**	
TE SAE (dr)	drug related, serious TEAE	**17%**	
TEAE (rdm)	resulting in dose modification	**72%**	
TEAE (rdd)	resulting in study drug discontinuation	**18%**	
TEAE (rdi)	resulting in study drug dose interruption	**66%**	
TEAE (rdr)	resulting in study drug dose reduction	**36%**	
on-study deaths	incidence (on study)	**12%**	
on-study deaths (dr)	incidence (on study), related to study drug	**0.7**	
Important AEs			
GI Diarrhoea Stomatitis	incidence of TEAE	**98%** 94% 33%	ISS
Skin-related Rash Dry Skin	incidence of TEAE	**84%** 39% 31%	
Infections Paronychia	incidence of TEAE	**59%** 33%	
Blood/lymphatic Anaemia	incidence of TEAE	**37%** 29%	
Cardiac QTc prolongation	incidence of TEAE	**37%** 12%	
Respiratory Pneumonitis/ILD	incidence of TEAE	**53%** 4%	
Amylase/lipase increase	incidence of TEAE	**74 %**	

Abbreviations: AE = adverse events; CR = complete response; GI = gastrointestinal; ILD = interstitial lung disease; IRC = independent review committee; ISS = integrated summary of safety; QTc = QT interval with correction method; SAE = serious adverse event; SAT = single-arm trial; SCS = summary of clinical safety; TE = treatment emergent; TEAE = treatment emergent adverse events

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Favourable effects

Study AP32788-15-101, which is the single pivotal study supporting the application, is an uncontrolled, open-label phase 1/2 study. The indication applied for is based on a post-hoc defined subpopulation of the pivotal study ('pooled prior platinum analysis set'). Due to the non-randomised/single-arm open-label design, the risk of bias (especially selection bias) cannot be eliminated. The study was multiply analysed and fundamentally amended based on this data and no null hypothesis was tested. In summary, data provided from study AP32788-15-101 are highly exploratory and level of evidence is low.

Due to limited life expectancy, overall survival (OS) represents the best endpoint to inform benefit/risk evaluation in the target population. The impact of treatment on OS, however, cannot be disentangled from prognostic factors. Therefore, a treatment effect on OS can be established only in comparison to an adequate control. Thus, OS results from the proposed pivotal study AP32788-15-101 must remain descriptive and non-inferential.

In contrast, ORR only occurs rarely in the absence of active treatment. Therefore, all ORR seen in a SAT can be ascribed to the test agent. Consequently, ORR must be the basis for the inference of a potential clinical benefit from the presented pivotal SAT. However, it is noted, that ORR is not an established surrogate endpoint for OS in NSCLC. Due to these limitations and uncertainties of ORR as a pivotal endpoint, the results in terms of ORR must be outstanding in relation to what can be achieved with existing therapeutic options.

In this specific case of SAT AP32788-15-101 the reported cORR (IRC) (28.1%, 95% CI (20.1, 37.3)) suggests promising clinical activity of mobocertinib monotherapy in the studied population that should be confirmed. These results are below what could be considered 'outstanding', also in relation to available therapies. Interestingly, in the pre-specified pivotal study population (i.e. part 3 full analysis set, extension phase) primary endpoint cORR (IRC) was even 2% lower than in the post-hoc defined 'pooled prior platinum analysis set'. Thus the most important condition for acceptance of study AP32788-15-101 to provide evidence for clinically relevant efficacy is not fulfilled (MO). Furthermore, the uncertainties in the efficacy estimate with a low level of evidence of the exploratory data provided make the interpretation challenging.

The median DoR, measured by BICR, was approximately 16 months in the pooled prior platinum analysis set. Interpretation of the clinical relevance of this data is questionable due to the low number of responses reached in the pivotal study and the explorative nature of the data provided.

Additional aspects

To support this uncontrolled clinical study data, the applicant performed study TAK-788-5002, a non-interventional (observational) retrospective study using longitudinal data from the Flatiron Health Research Database. The aim of this RWD analysis on patients with NSCLC and EGFR exon 20 insertion mutations was contextualisation of the pivotal SAT by providing a historical benchmark as supportive information. However, precise estimates cannot be provided from this study due to

- small patient numbers,
- differences between trial-aligned patients and patients from pivotal study part 3 regarding baseline/disease characteristics, and

- real-world response rates that were not in a clear different range than ORR reported for study AP32788-15-101 (95% confidence intervals for the rwORR based on trial-aligned and prior platinum trial-aligned patients overlap with the 95% CIs for cORR based on the respective - analysis populations from the pivotal SAT).

Due to the limitations of indirect comparisons, overlapping CIs should not be over-interpreted, but add to the uncertainties. Furthermore, response rates from study TAK-788-5002 were in a comparable range of response rates discussed in literature for existing treatment options. Therefore, a claim regarding the clinical meaningfulness of the outcomes from the SAT for mobocertinib based on the comparison to the RWD is impossible. The analyses directly comparing mobocertinib-treated patients to external RWD controls provide no added value to support the assessment, given the limitations of such an analysis where bias cannot not be excluded.

Unfavourable effects

With reference to the limitations of the small safety data pool submitted, for the safety results for mobocertinib it can be concluded, in accordance with the applicant, that mobocertinib has an acceptable safety and tolerability profile.

The present application has not revealed new severe safety issues that have not been previously described for this substance class, which is reassuring.

Most prominent are GI toxicity as TEAE of mobocertinib which is also common to immunotherapy, other EGFR TKIs, and might interfere with a patient's QoL. The mobocertinib safety profile, in terms of GI toxicity and specifically diarrhoea, is comparable to other EGFR TKIs.

Overall, the AEs noted with mobocertinib were consistent with the anticipated mechanism related safety profile of the EGFR TKI class, were manageable, reversible, and generally resolved with standard symptomatic measures, or dose modification and/or drug discontinuation. Results over time indicate that prolonged treatment with mobocertinib had acceptable tolerability. In the light of the immaturity of the available data with few patients and limited study duration, it cannot at present be concluded that mobocertinib has a better toxicity profile in some aspects than other EGFR TKIs indicated for NSCLC.

Of specific concern, since observed just in the small safety population available for mobocertinib but consistent with EGFR TKI class effects, are heart failure (including a fatal case), QT prolongations (including a case of Torsade de pointes), and ILD (including a fatal case). It appears that mobocertinib may be associated with a higher risk of cardiac toxicity/QTc prolongation than other EGFR TKIs.

4.7.2. Balance of benefits and risks

Given the poor prognosis of patients with locally advanced or metastatic NSCLC, the treatment effect of orally administered mobocertinib monotherapy is in principle considered clinically interesting and the safety profile appears manageable.

However, it is not possible to conclude that clinical benefit has been established based on the exploratory low level of evidence data presented. cORR (IRC) results from uncontrolled AP32788-15-101 are not considered outstanding, also in relation to available therapies. Due to the single-arm nature of the trial and the lack of formal hypothesis testing, OS results from AP32788-15-101 remain descriptive and non-inferential.

4.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

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

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

The product is not considered to fulfil the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive.

  Criterion currently not fulfilled. See BR assessment above.

- It is likely that the applicant will be able to provide comprehensive data.

  Criterion currently not fulfilled. As confirmatory study and specific obligation (SOB), the applicant proposes the ongoing randomised controlled open-label phase 3 study TAK-788-3001 comparing mobocertinib monotherapy versus pemetrexed-platinum–based chemotherapy in patients with treatment-naïve (i.e. 1st-line setting) NSCLC with EGFR exon 20 insertion mutations. The primary endpoint is PFS. The study has been designed to enrol approximately 318 patients. One-way cross-over to the experimental arm is allowed at progression.

  This study will provide data on mobocertinib monotherapy in an earlier line of treatment. If positive, this could support the implication of observed ORR on time-to-event outcomes, while not formally "confirming" the ORR results from the present study. The randomised design will allow isolation of drug effects (ADRs) from symptoms of disease, which will add to the current safety information based on SAT data. Feasibility problems can be expected for an intended RCT in an already approved indication. Therefore, the proposed SOB in an earlier treatment line is considered in principle acceptable. Enrolment is expected to be completed in third quarter 2022, interim PFS analysis in fourth quarter 2022, final PFS analysis and final OS analysis in fourth quarter 2023. The interim analysis for efficacy is planned after 50% (159 of 318) PFS events will be observed. Also this could in principle be acceptable. However, whether this study will in the end be accepted as SOB for this proposed CMA will depend on further details on the phase 3 study being requested regarding the interim analysis for efficacy that was not supported in a CHMP scientific advice in 2019 (EMEA/H/SA/3828/1/FU/1/2019/II) (MO).

- Unmet medical needs will be addressed

  Criterion currently not fulfilled. With the exception of those patients found to have low frequency insertion mutations, such as A763_Y764insFQEA, most patients with NSCLC harbouring EGFR exon 20 insertion mutations (~95%) are usually resistant to first and second-generation EGFR TKIs erlotinib, gefitinib, afatinib, or dacomitinib (NCCN guideline, NSCLC, Version 6.2021). The third generation EGFR TKI osimertinib has also been evaluated in a small single-arm trial in patients with NSCLC with EGFR exon 20 insertion mutations, and showed some interesting activity [Veggel et al 2020, Piotrowska et al 2020].

  However, patients with metastatic NSCLC (adenocarcinoma) harbouring EGFR exon 20 insertion mutations are usually treated as patients without a driver mutation. Initial treatment usually consists of carboplatin or cisplatin in combination with pemetrexed with or without an immune checkpoint (PD-1/PD-L1) inhibitor. Subsequent therapy options include systemic immune checkpoint inhibitor monotherapy (if no previous IO) or (independent of previous IO)

monotherapy with docetaxel, pemetrexed, gemcitabine or combination therapy with ramucirumab/docetaxel (NCCN 6.2021 - NSCLC).

Lately, in the EU Amivantamab received CMA in December 2021. Its role in treatment is to be clarified.

While there is certainly an unmet need for better treatment options, treatment options are available in the EU. Therefore, mobocertinib needs to show 'fulfilment of the unmet medical need' / a major therapeutic advantage over these existing therapies (including Amivantamab) in the context of CMA.

Note: Medicinal products with a positive benefit-risk balance, a differential safety profile, the convenience of oral administration, and the provision of a treatment alternative with a novel mechanism of action could provide a major therapeutic advantage (over authorised products) to patients provided it translates into a clinical benefit.

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

  Criterion not fulfilled. The applicant should provide a justification that the benefits to public health of the immediate availability of mobocertinib outweighs the risks inherent in the fact that additional data are still required

Scope of the indication

The sought wording of indication specifies both patients with locally advanced disease and metastatic disease. Since the indication covers patients who previously have received systemic therapy in the incurable setting, the term "locally advanced or metastatic" was adapted to "advanced".

In the current wording of indication, it is not entirely clear whether patients previously treated with platinum-based chemo-immunotherapy, which is likely the favoured first-line therapy today, are included. Notably, for the pooled prior platinum analysis set, all patients had received prior platinum-based chemotherapy, whereas 43 % had received immunotherapy. However, it is unclear to what extent immunotherapy was administered concomitantly with platinum-based chemotherapy, or if it was administered as different lines of treatment (the median number of prior lines of therapy was 2 (range 1-7)). Still, the data set indicates a similar efficacy for patients with or without previous treatment with immunotherapy. Therefore, an indication encompassing also patients having received immunotherapy in combination with chemotherapy is considered appropriate. Thus, the word "chemo" from the indication wording initially applied for was removed and was changed to "who have received prior platinum-based therapy".

4.8. Conclusions

From the quality point of view, the benefit/risk is positive provided that all other concerns regarding quality would be solved.

However, regarding the clinical part the benefit/risk balance is currently considered negative. Major objections exist concerning (i) benefit in the intended target population is not sufficiently justified and (ii) CMA criteria are not fulfilled.