STATISTICAL ANALYSIS PLAN

NCT Number: NCT04056468

Study Title: Phase 1 Pharmacokinetics and Safety Study of Oral Mobocertinib in Subjects With Moderate or Severe Hepatic Impairment and Normal Hepatic Function

Study Number: TAK-788-1008

SAP Version and Date:

Version 2.0: 12-Apr-2022

STATISTICAL ANALYSIS PLAN

Study Number: TAK-788-1008

Celerion Study Number: CA27459

Study Title: Phase 1 Pharmacokinetics and Safety Study of Oral Mobocertinib in Subjects with Moderate or Severe Hepatic Impairment and Normal Hepatic Function

Phase: 1

Version: Final Version 2

Date: 12-Apr-2022

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Based on:

Protocol Version: Amendment 2

Protocol Date: 07-Aug-2020

[redacted]

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Final	27-Jan-2021	Not Applicable
Final Version 2	12-Apr-2022	Updated following completion of the ad hoc topline pharmacokinetic analysis conducted to compare the total combined molar exposure of mobocertinib, AP32960, and AP32914 between the moderate hepatic impairment group and the normal hepatic function group as of a 29 June 2021 data cut-off date, and following the enrollment of Arm 3.

1.1 Approval Signatures

Electronic signature can be found on the last page of this document.

Study Title: Phase 1 Pharmacokinetics and Safety Study of Oral Mobocertinib in Subjects with Moderate or Severe Hepatic Impairment and Normal Hepatic Function

Approvals:

[redacted], PhD
[redacted], Statistical and Quantitative Science
Takeda Pharmaceuticals

Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 ABBREVIATIONS

λ_z	terminal disposition phase rate constant
AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
AUC_{∞}	area under the concentration versus time curve from time 0 extrapolated to infinity for total analyte
$AUC_{\infty,u}$	area under the concentration versus time curve from time 0 extrapolated to infinity for unbound analyte
AUC_{last}	area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration for total analyte
$AUC_{last,u}$	area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration for unbound analyte
BLQ	below the lower limit of quantitation
BOCF	baseline observation carried forward
CI	confidence interval
CL/F	apparent clearance after extravascular administration for total analyte
CL_u/F	apparent clearance after extravascular administration for unbound analyte
C_{max}	maximum observed plasma concentration for total analyte
$C_{max,u}$	maximum observed plasma concentration for unbound analyte
COVID-19	coronavirus disease 2019
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CV%	arithmetic percent coefficient of variation
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
Geom CV%	geometric percent coefficient of variation
Geom Mean	geometric mean
HI	hepatic impairment
IRC	Internal Review Committee
LSM	least-squares mean
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations
NCI ODWG	National Cancer Institute Organ Dysfunction Working Group
PK	pharmacokinetic(s)
PO	per os (by mouth)
PT	Preferred Term (MedDRA)
SAE	serious adverse event
SAP	statistical analysis plan

SD	standard deviation
SEM	standard error of the mean
SOC	System Organ Class
$t_{½z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time of first occurrence of C_{max} and $C_{max,u}$
V_z	apparent volume of distribution during the terminal disposition phase after extravascular administration for total analyte
$V_{z,u}/F$	apparent volume of distribution during the terminal disposition phase after extravascular administration for unbound analyte

4.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

4.1 Objectives

4.1.1 Primary Objective

To characterize the single-dose plasma pharmacokinetics (PK) of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with moderate and/or severe hepatic impairment (HI) compared to matched-healthy subjects with normal hepatic function.

4.1.2 Secondary Objectives

1. To evaluate plasma protein binding of mobocertinib and its active metabolites (AP32960 and AP32914).
2. To assess the safety of mobocertinib following a single oral dose in subjects with moderate and/or severe HI as well as matched-healthy subjects with normal hepatic function.

4.1.3 Exploratory Objective

[redacted]

4.2 Endpoints

4.2.1 Primary Endpoints

The primary endpoints of the study are the following total and unbound PK parameters for mobocertinib and its active metabolites, AP32960 and AP32914 (total and unbound parameters in parenthesis, respectively):

- Maximum observed concentration (C_{max} and $C_{max,u}$).
- Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞} and $AUC_{\infty,u}$).
- Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last} and $AUC_{last,u}$).
- Time of first occurrence of C_{max} (t_{max}).
- Terminal disposition phase half-life ($t_{½z}$).
- Terminal disposition phase rate constant (λ_z).
- Apparent clearance after extravascular administration (CL/F and CL_u/F) for mobocertinib only.
- Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F and $V_{z,u}$/F) for mobocertinib only.

4.2.2 Secondary Endpoints

Pharmacokinetics

Plasma protein binding of mobocertinib and its active metabolites (AP32960 and AP32914).

Safety

- Incidence of treatment-emergent adverse events (TEAEs) assessments (including physical examination findings).
- Clinical laboratory testing.
- 12-lead electrocardiogram (ECG).
- Vital signs.

4.2.3 Exploratory Endpoint

[redacted]

4.3 Estimand(s)

Not applicable.

5.0 STUDY DESIGN

This is an open-label, parallel-arm study of oral mobocertinib designed to assess the PK of single dose mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with moderate and/or severe HI compared to matched-healthy subjects with normal hepatic function.

The planned doses of mobocertinib per study arm are outlined in Table 5:1.

Table 5:1 Study Arms and Planned Dose

Study Arms				
Arm	**Number of Subjects**	**Classification**	**Child-Pugh Category (a)**	**Dose (b)**
1	8	Moderate	B	40 mg
2	8	Severe	C	40 mg (may have been reduced) (d)
3	8/8 (d)	Matched Healthy (c)		40 mg (n=8)/reduced dose to match dose in Arm 2, if needed (n=8) (d)

(a) Refer to Section 4.3 of protocol amendment 2 for the classification system.

(b) Single orally administered dose at Hour 0 on Day 1. Subjects were enrolled in a staggered manner beginning with approximately 3 subjects in the moderate impairment arm followed by approximately 3 subjects in the matched-normal hepatic function arm.

(c) Healthy subjects with normal hepatic function were recruited to match both moderate and severe HI arms by age (mean ± 10 years), gender (± 2 subjects per gender), and body mass index (BMI, mean ± 10%).

(d) If the dose of Arm 2 was reduced, then an additional 8 healthy matched subjects were to be dosed in Arm 3 at the corresponding dose level to Arm 2.

The study consists of a 21-day screening period, a 10-day confinement period (Day −1 to Day 10) and a follow-up phone call 30 ± 2 days after dosing.

Subjects were enrolled in a staggered manner. All subjects who qualified for the moderate HI arm may have been enrolled concurrently; however, approximately 3 subjects in the moderate HI arm and approximately 3 subjects in the matched-normal hepatic function arm must have completed up to Day 10 study procedures prior to enrolling subjects to the severe HI arm. An informal preliminary PK data analysis of these subjects was performed and may have additionally leveraged historical control PK data in healthy subjects to gain an initial estimate of the effect of moderate HI on the PK of mobocertinib and its active metabolites (AP32960 and AP32914). These preliminary data along with safety data guided the decision to enroll the severe HI arm at the same dose as the moderate HI arm. Following completion of enrollment of the moderate and severe HI arms, the remaining subjects were enrolled to the matched-normal hepatic function arm.

Subjects received a single oral dose of 40 mg mobocertinib on Day 1 (Table 5:2).

Table 5:2 Study Design

Study Day	**Screening**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Mobocertinib PO			X									
PK Blood Samples			X	X	X	X	X	X		X		X
[redacted]												
Confinement in CRU		X	X	X	X	X	X	X	X	X	X	X

CRU-clinical research unit; PK-pharmacokinetics; PO-per os (by mouth).

Blood samples were to be collected from Days 1 to 10 at predetermined time points to characterize the PK and plasma protein binding of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with moderate and/or severe HI compared to matched-healthy subjects with normal hepatic function.

Subjects were confined in the clinical research unit (CRU) until the morning of Day 10 after the 216-hour PK sample. A subject may have been required to remain at the CRU for longer periods, at the discretion of the Investigator. Subjects may have been admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per CRU requirements.

A final safety follow up phone was made 30 ± 2 days after mobocertinib dosing to determine if any adverse events (AEs) have occurred since last study visit.

6.0 STATISTICAL HYPOTHESES AND DECISION RULES

6.1 Statistical Hypotheses

Not applicable.

6.2 Statistical Decision Rules

Not applicable.

6.3 Multiplicity Adjustment

Not applicable.

7.0 SAMPLE-SIZE DETERMINATION

The planned sample size of 8 subjects in each hepatic function arm represents a size that is considered adequate to provide a descriptive characterization of the PK of mobocertinib and its active metabolites in subjects with moderate or severe hepatic impairment compared to healthy subjects with normal hepatic function.

At least 24 subjects were to be enrolled into 3 arms (approximately 8 subjects in each arm) in the study. The target number for the matched-healthy subjects with normal hepatic function was 8 subjects; however, up to 16 healthy subjects may have been enrolled into Arm 3 if it was not feasible to match the first 8 healthy subjects into both Arms 1 and 2.

8.0 ANALYSIS SETS

8.1 Safety Analysis Set

All subjects who received the study drug will be included in the safety evaluations.

8.2 Pharmacokinetic Analysis Set

Samples from all subjects will be assayed even if the subjects do not complete the study. All subjects who comply sufficiently with the protocol-specified dosing and display an evaluable PK profile (eg, exposure to treatment, availability of sufficient PK measurements and absence of major protocol violations) will be included in the statistical analyses. Any subject who experiences emesis within 8 hours post dosing with mobocertinib may be included in the PK analysis but excluded from the statistical analysis.

9.0 STATISTICAL ANALYSIS

9.1 General Considerations

All PK analyses will be conducted using Phoenix® WinNonlin® Version 8.1, or higher. All statistical analyses will be conducted using SAS® Version 9.4. All relevant data recorded in the electronic case report form (eCRF) will be listed by subject. All tables, figures, and listings (TFLs) shells and numbering list will be included and specified in the TFL Shells document.

Concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are obvious outliers (e.g., BLQ value between measurable values), in which case they will be treated as missing.

A subject's PK parameter data will be included in the listings but excluded from the descriptive statistics and statistical analyses if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that subject's maximum concentration value in that period
- A subject did not meet inclusion/exclusion criteria that may have an effect on PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A subject deviates substantially from the protocol-defined study procedures, including but not limited to dosing, dose timing, sample collection, etc (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)

The details on PK parameter calculations and TFLs will be outlined in the Clinical Pharmacology Analysis Plan (CPAP) and TFL Shell document including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2z}$ value and other λ_z-dependent parameters
- PK parameters presented by hepatic function group, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables

- Concentration data presented by hepatic function group, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter WinNonlin® output file used to generate the TFLs
- Analysis of variance (ANOVA) results presented in in-text and end-of-text tables
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures
- Individual concentration-time figures.

All concentration and PK parameter data and their descriptive statistics (with the exception of the number of observations) will be presented to 3 significant digits. The number of observations (n) will be presented as an integer (no decimal places).

For demographic and safety data where appropriate, variables will be summarized descriptively. For the categorical variables, the count and proportions of each possible value will be tabulated, where applicable. The denominator for the proportion will usually be based on the number of subjects dosed. For continuous variables, the number of subjects with non-missing values, mean, geometric mean, % CV of geometric mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers.

9.1.1 Handling of Treatment Misallocations

Not applicable.

9.2 Study Information

A study information table will be generated including the following items: date of first subject's signed informed consent form, date of first dose, date of last dose, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Dictionary, and SAS version used for creating the datasets.

9.3 Disposition of Subjects

Disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized by hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function) and overall. Study completion status, including reason for discontinuation, will also be listed by subject.

9.4 Demographic and Other Baseline Characteristics

9.4.1 Demographics

Demographic and baseline characteristics will be summarized descriptively by hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function) and overall. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [recorded in the eCRF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI recorded at screening will be used in the baseline summaries. Demographics data will also be listed as recorded in the eCRF, including the date of informed consent.

9.4.2 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing the informed consent form (ICF). Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug(s) will be classified as an adverse event. All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 23.0. If appropriate, the medical history listing will include whether the event was medical or surgical, the body system or organ class involved, coded term, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

9.4.3 Baseline Characteristics

Child-Pugh scores will be assessed at screening to classify subjects into hepatic function arms. The overall scores will be summarized by hepatic function arm. Individual results will be listed by hepatic function arm and subject.

9.5 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and safety evaluation stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than study drug taken at any time between Day 1 through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the WHO Drug Dictionary March 2020 B3 Global and listed. If appropriate, the listing will include the medication name, coded term, dosage, route of administration, start date and end date, or whether it continued after study completion, and indication for use.

9.6 Efficacy Analysis

Not applicable.

9.7 Safety Analysis

For each hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function) safety and tolerability will be assessed through incidence, severity and type of adverse events. Safety will also be assessed through changes from baseline in subjects' vital signs, safety ECGs and clinical laboratory assessments; along with symptom-driven physical examinations. All safety data will be listed by hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function), subject, and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

9.7.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity, relationship to study drug (related or not related) and action relative to the study drug as recorded in the eCRF. All AEs occurring during this study will be coded using the MedDRA® Dictionary Version 23.0. However, only TEAEs occurring after dosing will be summarized. A TEAE is defined as any AE newly occurring or worsening from the first dose until a follow-up phone call 30 days (±2 days) after the last dose of study drug. If a subject experiences an exacerbation or complication of a concurrent medical condition that should be recorded as an AE.

All AEs, including TEAEs, will be severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, with grading levels 1 to 5 which correspond to mild, moderate, severe or medically significant but not immediately life-threatening, life-threatening consequences, and fatal.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summaries will be presented by hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function). Summary tables will include number of subjects reporting the AE and as percent of safety analysis set by hepatic function group (ie, Moderate HI, Severe HI, Normal Hepatic Function) and overall. The most commonly reported non-serious TEAEs (i.e., those events reported by >5% of all subjects in each hepatic function arm, excluding serious adverse events [SAEs]) will also be summarized. In addition, TEAEs will be summarized as number of AEs and percentage of AEs for each hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function) for the overview of TEAEs.

Additional TEAE summary tables will be presented by severity and relationship to study drug.

Should any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAE. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the CSR.

In summary, AEs will be summarized by each hepatic function group and overall as follows:

- Overview of TEAEs - number and percentage of subjects, number of events;
- TEAEs by system organ class (SOC), and preferred term (PT) - number and percentage of subjects;
- Most frequent TEAEs by PT [excluding SAEs] (sorted by frequency, occurring in ≥5% of subjects in any hepatic function arm) - number and percentage of subjects;
- TEAEs by relationship to study drug and by SOC, and PT - number and percentage of subjects;
- TEAEs by severity and by SOC, and PT - number and percentage of subjects;
- TEAEs for severity grade 3 or higher by relationship and by SOC, and PT - number and percentage of subjects;
- TEAEs leading to study discontinuation by SOC, and PT - number and percentage of subjects;
- Serious TEAEs by SOC, and PT - number and percentage of subjects;
- Serious TEAEs by relationship to study drug and by SOC, and PT - number and percentage of subjects;
- Serious TEAEs by severity and by SOC, and PT - number and percentage of subjects;
- TEAEs resulting in death by PT - number and percentage of subjects;

Key guidelines for determining the incidence of AEs are as follows:

- AEs with missing or unknown severity will be considered as severe (or Grade 3).
- AEs with missing or unknown relationship to study drug will be counted as related.
- AEs with missing date will be counted as treatment-emergent, unless the date is known to be prior to dosing.
- AEs with a start date on Day 1 but missing start time will be counted as treatment-emergent.
- A subject with 2 or more AEs within the same level of the MedDRA term will be counted only once in that level.
- SOCs will be sorted in alphabetical order. Within an SOC, PTss will be sorted in descending order of total number of subjects with the preferred term among all the hepatic function arms.
- For the summary of TEAEs by SOC and PT and severity, if a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the

maximum severity grade of the episode (preferred term). Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once by the maximum severity in that SOC.

- In selected summaries, adverse events will be summarized by the number of events reported in addition to the number and percentage of subjects with events.

Data listings for TEAEs, TEAEs leading to study discontinuation, SAEs, and deaths will be presented. The AEs will be listed by hepatic function arm, subject number, and onset date of the adverse event. The listing will contain: subject identifier, adverse event (PT and reported term), SOC, onset date, end date or whether the event was ongoing, duration, frequency, severity, action taken concerning study drug, causality to study drug, the outcome, whether the adverse event was a SAE.

9.7.2 Adverse Events of Special Interest (if applicable)

Not applicable.

9.7.3 Clinical Laboratory Assessments

Hematology, serum chemistry, coagulation, and urinalysis will be performed at screening, check-in (Day -1), Day 3, and Day 10 (or at early termination if applicable). Urine drug screening will be carried out at screening and check-in (Day-1) only. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI).

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function) and assessment time points. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment including rechecks taken prior to dosing (generally Day -1). All clinical laboratory listings and tables will be presented in conventional units. Postdose unscheduled or recheck assessments will not be used in analysis.

For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above normal (H), normal (N), or below normal (L)) with the postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be listed with the corresponding categorical references as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. All clinically significant laboratory tests, as indicated by the PI, and the corresponding values will be listed by subject in a table. All clinical laboratory data will be presented in by-subject data listings.

9.7.4 Vital Signs

Vital sign measurements consist of body temperature, respiratory rate, BP, and HR. Temperature, respiratory rate will be collected at screening only. BP and HR will be collected at screening, prior to dosing on Day 1, Day 1 hours 4 and 12, Day 2 (24 Hours), and Day 10 (or at early termination if applicable). Additional unscheduled vital signs may be recorded at other times if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for HR and BP results and change from baseline by hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function) and time point of collection. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment, including rechecks (by replacement), taken prior to dosing. Postdose unscheduled or recheck assessments will not be used in analysis. Vital sign data will also be displayed in a data listing by subject.

9.7.5 Electrocardiograms

Single 12-lead ECGs will be collected at screening, prior to dosing on Day 1, Day 1 Hour 4, Day 2 (Hour 24), and Day 10 (or at early termination if applicable). Additional unscheduled ECGs may be recorded at other times if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from baseline by hepatic function arm (ie, Moderate HI, Severe HI, Normal Hepatic Function) and time point of collection. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment, including rechecks (by replacement), taken prior to dosing. Postdose unscheduled or recheck assessments will not be used in analysis. ECG data will also be displayed in a data listing by subject.

9.7.6 Physical Examination

Physical examination will be performed at screening and check-in. If the screening assessment was conducted within 4-7 days prior to dosing (Day 1), screening result may be used at the discretion of the PI. Symptom-driven physical exams may be performed at other times at the discretion of the PI. Physical exam findings will be presented in the data listings by arm and subject. Reproductive system findings will also be listed by subject.

9.7.7 Overdose

All cases of overdose will be presented in a data listing by subject. Any AEs associated with overdose will be documented as AEs.

9.7.8 Other Safety Analysis (if applicable)

Spirometry as the PFT may be performed in the event of a pulmonary AE, if deemed clinically necessary by the Investigator or designee.

9.7.9 Extent of Exposure and Compliance

The date, time, and treatment administered will be listed by subject.

9.8 Pharmacokinetic Analysis

Blood samples for the assessment of plasma mobocertinib, AP32960, and AP32914 concentrations and plasma protein binding will be collected as outlined in Table 9:1 below:

Table 9:1 Collection of Blood Samples for Pharmacokinetic and Plasma Protein Binding Analyses

Analyte	Matrix	Scheduled Time (Hours)*
Mobocertinib, AP32960, and AP32914	Plasma	Predose, and 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 168, and 216 hours postdose
Protein Binding	Plasma	2, 4, and 24 hours postdose

*The actual date and time of sample collection was recorded on the source document in the case report form.

Additional details regarding the PK analysis will be described in the CPAP for this study.

The ln-transformed Combined Molar $C_{max,u}$, Combined Molar $AUC_{last,u}$, and Combined Molar $AUC_{\infty,u}$ for mobocertinib and its metabolites (AP32960 and AP32914) will be compared between the HI groups and the matched healthy group using an analysis of variance (ANOVA) model.

The ANOVA model will include each HI versus healthy condition as a fixed effect. Each ANOVA analysis will calculate the least-squares means (LSMs), the difference between group LSMs, and the standard error associated with the difference. Residual variance will be reported. Ratios of LSMs and 90% confidence intervals will be calculated using the exponential function of the difference between group LSMs from the analysis on the ln-transformed Combined $C_{max,u}$, Combined $AUC_{last,u}$, and Combined $AUC_{\infty,u}$. The above analysis will also be performed on the ln-transformed Combined C_{max}, Combined AUC_{last}, and Combined AUC_{∞}.

The same analysis will be repeated for each analyte (mobocertinib, AP32960, and AP32914) separately and will be performed on both unbound ($C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$) and total (C_{max}, AUC_{last}, and AUC_{∞}) PK parameters. Additional ANOVA analyses may also be performed stratifying patients using the National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) criteria for hepatic function.

The following SAS® code will be used to perform the analysis:

```
PROC MIXED DATA=XXX;
CLASS Arm;
MODEL <ln_pkparam>=Arm/DDFM=KR;
ESTIMATE 'Moderately Impaired vs. Matched Healthy' Arm 1 0 -1 / CL ALPHA=0.1 E;
ESTIMATE 'Severely Impaired vs. Matched Healthy' Arm 0 1 -1 / CL ALPHA=0.1 E;
LSMEANS Arm;
RUN;
```

Where 'Arm' is as described in Table 5:1, ie, 1=Moderate, 2=Severe, 3=Healthy

9.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

9.10 Preliminary Analyses

No preliminary analyses will be performed.

9.11 Interim Analyses

An informal preliminary PK data analysis was to be performed on approximately 3 moderate HI subjects and 3 healthy matched subjects who completed study procedures up to Day 10 and may have additionally leveraged historical control PK data in healthy subjects to gain an initial estimate of the effect of moderate HI on the PK of mobocertinib and its active metabolites (AP32960 and AP32914). These preliminary data along with safety data were to guide the decision to enroll the severe HI arm (for example, a decision was to be made to dose the severe HI group at the same dose as the moderate HI arm, a reduced dose, or to not dose this arm).

To address a specific request from a regulatory agency, an ad hoc topline PK analysis was conducted to compare the total combined molar exposure of mobocertinib, AP32960, and AP32914 between the moderate HI group (n=8) and the normal hepatic function group (n=6) as of a 29 June 2021 data cut-off date.

There are no predetermined criteria for early termination of the study.

9.12 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

10.0 REFERENCES

Not applicable.

11.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Protocol Amendment 2 stated that the ANOVA model will include HI versus normal conditions as a fixed effect and subject nested within group as a random effect. However, the random effect was not needed since we only have one measurement (eg, Combined $C_{max,u}$) per subject per analysis. Therefore, "CLASS Arm Subject;" was replaced with "CLASS Arm" and "RANDOM Subject(Arm);" was removed from the model.

12.0 APPENDIX

12.1 Changes From the Previous Version of the SAP

Not applicable.

12.2 Data Handling Conventions

Not applicable.

12.3 Analysis Software

SAS® Version 9.4 will be used for all statistical analysis provided in the CSR.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	12-Apr-2022 21:22 UTC