CLINICAL STUDY PROTOCOL

NCT Number: NCT04056455

Study Title: A Phase 1 Pharmacokinetic Study of Oral Mobocertinib in Subjects With Severe Renal Impairment and Normal Renal Function

Study Number: TAK-788-1007

Protocol Version and Date:

Version 2.0: 14-December-2020

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1 Pharmacokinetic Study of Oral Mobocertinib in Subjects with Severe Renal Impairment and Normal Renal Function

Study Identifier: TAK-788-1007

Compound: Mobocertinib (TAK-788)

Date: 09 December 2020

Version/Amendment Number: Amendment 2

Amendment History:

Date	Amendment Number	Amendment Type	Region
12 July 2019	Initial Version	Not applicable	United States
05 Aug 2020	01	Appendix E	United States
09 December 2020	02	Appendix F	United States

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge, Massachusetts USA 02139 Telephone: +1 (617) 679-7000	Mobocertinib (TAK-788)
Study Identifier: TAK-788-1007 (CA27460)	**Phase:** 1
Protocol Title: A Phase 1 Pharmacokinetic Study of Oral Mobocertinib in Subjects with Severe Renal Impairment and Normal Renal Function	

Study Design:

This is an open-label, parallel-arm study of oral mobocertinib designed to assess the PK of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe renal impairment (RI) compared to matched-healthy subjects with normal renal function.

Approximately 12 subjects will be enrolled in each arm of the study according to the following criteria:

- Arm 1: Severe RI (estimated glomerular filtration rate [eGFR] 15-29 mL/min),
- Arm 2: Normal renal function (eGFR ≥90 mL/min). Healthy subjects with normal renal function will be recruited to match subjects with severe RI by age (mean ± 10 years), gender (± 2 subjects per gender), and body mass index (BMI) (mean ± 10%).

The study will consist 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.

For assessment of renal function at screening, eGFR will be based on the eGFR value calculated from Modification of Diet in Renal Disease (MDRD) formula divided by standard body surface area (BSA) value of 1.73 m^2 for the renal classification category of subjects (ie, severe RI or normal renal function). For subjects with non-standard BSA, the eGFR value calculated by MDRD formula will be multiplied by the individual's BSA calculated using appropriate formula (Dubois and Dubois, 1916) and divided by 1.73 m^2. The eGFR value will be compared to the renal function assignment from historical values within a 6 month period from screening. The subjects to be recruited into this study should show a stable renal function, such as <30% difference in eGFR values, within 6 months from screening. If the renal function of historical and screening assessments falls in the same renal function category with <30% difference, the subject can be enrolled into this study if other inclusion criteria are met and none of the exclusion criteria are met. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (at least 72 hours apart) and the two values have to show <30% difference and fall in the same renal function category of either severe RI or normal renal function before check-in. If the results of the 2 most recent assessments are not in agreement with regard to the subject's renal function category, the third assessment has to be performed at least 72 hours after the second assessment. If the second and third measurements differ, the subject will not be eligible for the study.

Subjects will receive a single oral dose of 80 mg mobocertinib capsule on Day 1 (Table 1.a).

Table 1.a Study Design for Arms 1 and 2

	-1	1	2	3	4	5	6	8	10
Mobocertinib PO		X							
PK Blood Samples		X	X	X	X	X	X	X	X
PK Urine Samples		X	X	X	X	X	X		
Confinement in CRU	X	X	X	X	X	X	X	X	X

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

Blood samples will be collected from Days 1 to 10 and urine samples will be collected from Day 1 to the morning of Day 6 at predetermined time points to characterize the plasma and urine PK and plasma protein binding of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe RI and in matched-healthy subjects with normal renal function.

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

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

A final safety follow up phone call will occur 30 ± 2 days after mobocertinib dosing to determine if any AEs have occurred since last study visit.

Study Objectives:

Study Primary Objective:

To characterize the single-dose plasma and urine PK of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe RI compared to matched-healthy subjects with normal renal function.

Study 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 single oral dose in subjects with severe RI and the matched healthy subjects with normal renal function.

Study Subject Population: Adult male and female subjects will be enrolled into one of the 2 arms of the study according to the following criteria:

Arm 1: Severe RI (eGFR 15-29 mL/min).

Arm 2: Normal renal function (eGFR ≥90 mL/min).

Planned Number of Subjects:	**Planned Number of Sites:**
A total of approximately 24 adult male and female subjects will be enrolled into 2 arms of the study. Twelve (12) subjects with severe RI will be enrolled to Arm 1. Twelve (12) matched-healthy subjects with normal renal function will be enrolled to Arm 2.	At least 2
Dose Level:	**Route of Administration:**
80 mg mobocertinib single dose	Oral
Duration of Treatment:	**Planned Study Duration:**
Day 1, subjects will receive a single oral dose of mobocertinib.	Approximately 51 days ± 2 days including screening period and follow-up.

Criteria for Inclusion:

Healthy Subjects

All healthy subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult male or female subjects aged ≥18 to <81 years, at screening. Subjects will be matched to RI subjects by age (mean ± 10 years) at screening.
2. Continuous non-smoker or moderate smoker (≤10 cigarettes/day or the equivalent) before screening. Subject must agree to consume no more than 5 cigarettes or equivalent/day from the 7 days prior to mobocertinib dosing and throughout the period of PK sample collection.
3. Body mass index (BMI) ≥18.0 and ≤39.0 kg/m^2, at screening. Subjects will be matched to RI subjects by BMI (mean ± 10 %) at screening. At least 50% of the subjects will be required to be of BMI ≥18.0 and ≤35.0 kg/m^2, at

screening.

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee. Has liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin within the upper limit of normal at screening and at check-in.
5. Baseline eGFR ≥90 mL/min based on the MDRD equation at screening divided by standard BSA value of 1.73 m^2). For subjects with non-standard BSA, the eGFR value calculated by MDRD formula will be multiplied by the individual's BSA calculated using appropriate formula and divided by 1.73 m^2.
6. Female subjects of nonchildbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing:
   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status.
7. Female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 30 days following the mobocertinib dosing as indicated in Appendix D.
8. Female subjects must agree not to donate ova/oocytes during the study and for at least 30 days following mobocertinib dosing as indicated in Appendix D.
9. Males subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in Appendix D or abstain from sexual intercourse during the study until at least 30 days following mobocertinib dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with his preferred and usual lifestyle.
10. Male subjects must agree not to donate sperm from dosing until at least 30 days following mobocertinib dosing as indicated in Appendix D.
11. Understands the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol.

Subjects with Renal Impairment

All RI subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Adult male or female subjects aged ≥18 to <81 years, at screening.
2. Continuous non-smoker or moderate smoker (≤10 cigarettes/day or the equivalent) before screening. Subject must agree to consume no more than 5 cigarettes or equivalent/day from the 7 days prior to dose of mobocertinib and throughout the period of PK sample collection.
3. Body mass index BMI ≥18.0 and ≤39.0 kg/m^2, at screening. At least 50% of the subjects will be required to be of BMI ≥18.0 and ≤35.0 kg/m^2, at screening.
4. Aside from RI, be sufficiently healthy for study participation based upon medical history, physical examination, vital signs, ECGs, and screening clinical laboratory profiles, as deemed by the Investigator or designee.
5. Baseline eGFR of 15-29 mL/min not on dialysis based on the MDRD equation at screening divided by standard BSA value of 1.73 m^2. For subjects with non-standard BSA, the eGFR value calculated by MDRD formula will be multiplied by the individual's BSA calculated using appropriate formula and divided by 1.73 m^2.
6. Has a diagnosis of chronic (>6 months), stable (no significant changes in renal function [<30%] in the 30 days preceding screening; no acute episodes of illness within the previous 2 months due to deterioration in renal function) renal insufficiency. Subjects with RI may have related medical conditions consistent with their disease

(eg, mild diabetes) that are stable for at least 3 months prior to screening, in the opinion of the Investigator or designee.

7. For a female of nonchildbearing potential, must have undergone one of the following sterilization procedures at least 6 months prior to dosing:
   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status.
8. Female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 30 days following mobocertinib dosing as indicated in Appendix D.
9. Female subjects must agree not to donate ova/oocytes during the study and for at least 30 days following mobocertinib dosing as indicated in Appendix D.
10. Males subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in Appendix D or abstain from sexual intercourse during the study until at least 30 days following mobocertinib dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with his preferred and usual lifestyle.
11. Male subjects must agree not to donate sperm from dosing until at least 30 days following mobocertinib dosing as indicated in Appendix D.
12. Understands the study procedures in the ICF and be willing and able to comply with the protocol.

Criteria for Exclusion:

Healthy Subjects

All healthy subjects must be excluded from participating in the study if the subject:

1. Mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subjects by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
5. History or presence of clinically significant hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. History or presence of any previous significant lung disease except child asthma.
7. History of lung infection within 3 months of screening or ongoing lung infection.
8. Female subjects with a positive pregnancy test or who are lactating.
9. Positive results for urine or breath alcohol screen at screening or check-in.
10. Positive results for urine or saliva drug screen at screening or check-in unless the positive drug screen is due to prescription drug use that is approved by the Investigator and Sponsor.
11. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
12. Positive test result for novel corona virus disease 2019 (COVID-19) testing at screening or check-in.
13. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
14. Seated blood pressure is less than 90/40 mmHg or greater than 150/95 mmHg at screening.

15. QTcF interval is ≥450 msec in males or ≥470 msec in females or has ECG findings deemed abnormal with clinical significance by the Investigator or designee at screening.
16. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 7.3 (Prohibitions and Concomitant Medication) for the prohibited time period.
17. Been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to dosing and throughout the study.
18. Donation of blood or significant blood loss within 56 days prior to dosing.
19. Plasma donation within 7 days prior to dosing.
20. Participation in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.

Subjects with Renal Impairment

All RI subjects must be excluded from participating in the study if the subject:

1. Mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical, aside from RI, or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subjects by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
5. History or presence of clinically significant hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. History or presence of any previous significant lung disease except child asthma.
7. History of lung infection, within 3 months of screening or ongoing lung infection.
8. Fluctuating or rapidly deteriorating renal function within the screening period, and up to 30 days prior to Day 1, in the opinion of the Investigator and Sponsor.
9. Failed renal transplant or has had a nephrectomy.
10. Rapidly fluctuating renal function, as determined by historical measurements; or has demonstrated or suspected renal artery stenosis. Rapidly fluctuating renal function is defined as eGFR that differs by more than 30% within a 6 month period before the screening. If historical measurements are not available, then the 2 screening measurements will be used to demonstrate stability; a second baseline eGFR sample will be taken during the screening period (at least 72 hours apart) and the two values have to show <30% difference and fall in the same renal function category of either severe RI or normal renal function before check-in. If the results of the 2 most recent assessments are not in agreement with regard to the subject's renal function category, the third assessment has to be performed at least 72 hours after the second assessment. If the second and third measurements differ, the subject will not be eligible for the study.
11. Female subjects with a positive pregnancy test or who are lactating.
12. Positive results for urine or breath alcohol screen at screening or check-in.
13. Positive results for urine or saliva drug screen at screening or check-in unless the positive drug screen is due to prescription drug use that is approved by the Investigator and Sponsor.
14. Positive results at screening for HIV, HBsAg, or HCV.
15. Positive test result for COVID-19 testing at screening or check-in.
16. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
17. Seated blood pressure is less than 90/40 mmHg or greater than 180/100 mmHg at screening.
18. QTcF interval is >500 msec or has ECG findings deemed abnormal with clinical significance by the Investigator

or designee at screening.

19. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 7.3 (Prohibitions and Concomitant Medication) for the prohibited time period.
20. Been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to dosing and throughout the study.
21. Donation of blood or significant blood loss within 56 days prior to dosing.
22. Plasma donation within 7 days prior to dosing.
23. Participation in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.

Study Endpoints:

Primary Endpoints:

The following total and unbound PK parameters in plasma will be analyzed for mobocertinib and its active metabolites, AP32960 and AP32914 (bound 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 $AUC_{last,u}$)
- Combined molar unbound $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$ of mobocertinib, AP32960, and AP32914.
- 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.

The following urinary PK parameters will be analyzed for mobocertinib and its active metabolites, AP32960 and AP32914:

- Amount of drug excreted in urine from time 0 to time t (Ae_t)
- Fraction of administered dose excreted in urine from time 0 to time t ($f_{e,t}$)
- Renal clearance (CL_R)

Secondary Endpoints:

Pharmacokinetics:

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

Safety:

- Incidence of treatment emergent AEs (TEAEs) (including physical examination findings).
- Clinical laboratory values.
- 12-lead ECG.
- Vital signs

Statistical Considerations:

Pharmacokinetics:

The natural log (ln)-transformed combined molar unbound $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$, for mobocertinib and its metabolites (AP32960 and AP32914) will be compared between RI and the healthy arms using an analysis of variance (ANOVA) model.

The ANOVA model will include RI versus normal conditions as a fixed effect and subject nested within group as a random effect. Each ANOVA analysis will calculate the least-squares mean (LSM), the difference between group LSMs, and the standard error associated with the difference. Residual, subject nested within group, and intersubject variance will be reported. Ratio of LSM and 90% confidence interval (CI) will be calculated using the exponential function of the difference between group LSMs from the analysis on the ln-transformed combined molar unbound $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u,}$ for mobocertinib and its metabolite (AP32960 and AP32914). The same analysis will be repeated for each analyte (mobocertinib, AP32960, and AP32914) separately and will be performed on total PK parameters as well (C_{max}, AUC_{last}, and AUC_{∞}).

Safety:

Safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

Sample Size Justification:

The planned sample size of 12 subjects in each renal function arm is considered adequate to provide a precise estimation of the combined molar AUC_{∞} of mobocertinib and its active metabolites AP32960, and AP32914 in subjects with severe renal impairment compared to healthy subjects with normal renal function. The sample size calculation was based on the 95% confidence interval (CI) for the geometric mean of the combined molar AUC_{∞} of mobocertinib and its active metabolites AP32960, and AP32914. The average interpatient coefficient of variation for mobocertinib, AP32960, and AP32914 apparent clearance was estimated to be [redacted] With a sample size of 12 in each renal function arm, the 95% CI for the for the geometric mean of the combined molar AUC_{∞} is expected to be 0.6 to 1.4 with at least 80% power according to the variance assumptions.

2.0 STUDY SCHEMATIC

Screening	Treatment			Follow-up [a]
	Check-in and Predose Assessments	**Mobocertinib Dosing, PK Sampling, and Study Assessments**	**PK Sampling and Study Assessments**	
Within 21 days prior to dosing	Day -1	Day 1	Day 2-10	30 days ± 2 following mobocertinib dose
Outpatient Visit	Confinement [b]			

[a] The clinic will contact all subjects (including subjects who terminate the study early) 30 ± 2 days after the mobocertinib administration to determine if any adverse events have occurred since the last study visit.

[b] Subjects will start the confinement on Day -1 and be released from confinement after the 216-hour study assessments (Day 10) are complete, as per the scheduled of study procedures (Section 9.0). Subjects may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per CRU requirements. At all times, subject may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.

3.0 SCHEDULE OF STUDY PROCEDURES

Study Procedures [a]		**Study Days (Arm 1 and Arm 2)**																	
Days →	**S** [b]	**-1**	**1**								**2**		**3**	**4**	**5**	**6**	**8**	**10**	
Hours →		**C-I** [d]	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**168**	**216**	**FU** [c]
Administrative Procedures																			
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Medical History	X																		
Safety Evaluations																			
Full Physical Examination [e]	X	X [f]																X [g]	
Height	X																		
Weight	X	X [f]																	
Assessment of Renal Function [h]	X	X																	
12-Lead Safety ECGs	X		X [i]				X				X							X [g]	
Vital Signs (HR and BP)	X		X [i]				X			X	X							X [g]	
Vital Signs (RR and T)	X																		
Pulmonary Function Test [j]										X									
Hem, Serum Chem [k], and UA	X	X													X			X [g]	
Serum Pregnancy Test (♀only)	X	X																	
Serum FSH (PMP ♀ only)	X																		
Urine/saliva Drug Screen	X	X																	
Urine/breath Alcohol Screen	X	X																	
HIV/Hepatitis Screen	X																		
COVID-19 Test	X	X																	
AE Monitoring [j]										X									X
ConMeds Monitoring										X									
Study Drug Administration / PK																			
Mobocertinib Administration			X																
Blood for Mobocertinib and metabolites (AP32960 and AP32914) PK			X [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Procedures [a]	**S** [b]	**Study Days (Arm 1 and Arm 2)**																	
Days →		**-1**	**1**								**2**		**3**	**4**	**5**	**6**	**8**	**10**	
Hours →		**C-I** [d]	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**168**	**216**	**FU** [c]
Blood for Protein Binding for Mobocertinib and metabolites (AP32960 and AP32914)						X	X				X								
Urine for PK Mobocertinib and metabolites (AP32960 and AP32914)			X [m]																
Other Procedures																			
Confinement in the CRU [n]		X																	
Stool Sample for Microbiome [o]	X																		
Blood Sample for Blood Sample for Bacterial Antibodies and Other Circulating Biomarkers	X																		
Visit	X																		

a For details on Procedures, refer to Section 9.0.

b Within 21 days prior to study drug administration.

c The clinic will contact all subjects (including subjects who terminate the study early) 30 ± 2 days after mobocertinib administration to determine if any AEs have occurred since the last study visit.

d Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU. Subjects may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per CRU requirements

e Full physical examination will be conducted as indicated. Symptom-driven physical examination may be performed at other times, at the Investigator's or designee's discretion.

f If the screening assessment was conducted within 4-7 days prior to dosing (Day 1), assessment will be conducted at check-in only if, in the opinion of the Investigator, there is reason to believe they have substantially changed otherwise the screening value will be used.

g To be performed at Day 10 or prior to early termination from the study.

h For assessment of renal function at screening, eGFR will be calculated based on the eGFR value calculated by MDRD formula divided by standard BSA value of 1.73 m^2 for the renal classification category of subjects (ie, severe RI or normal renal function). For subjects with non-standard BSA, the eGFR value calculated by MDRD formula will be multiplied by the individual's BSA calculated using appropriate formula (Dubois and Dubois 1916) and devided by 1.73 m^2. The eGFR value will be compared to the renal function assignment from historical values within a 6 month period from screening. If the renal function of historical and screening assessments falls in the same renal function category, the subject can be enrolled into this study if other inclusion criteria are met. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (at least 72 hours apart) and the two values have to fall in the same renal function category of either severe RI or normal renal function before check-in. If the results of the two most recent assessments are not in agreement with regard to the subject's renal function category, the third assessment has to be performed at least 72 hours after the second assessment.

i To be performed within 24 hours prior to dosing.

j Pulmonary function test may be performed in the event of a pulmonary AE, if deemed clinically necessary by the Investigator or designee.

k Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample is being taken.

l To be performed prior to dosing.

m Urine collection intervals are: pre-dose (spot collection), 0 - 12 hours, 12 - 24 hours postdose, 24 -36 hours postdose, 36 -48 hours postdose, 48 -72 hours postdose, 72 -96 hours postdose, and 96 -120 hours post-dose. For subjects with renal insufficiency, urine samples will be collected whenever possible, as they may not be able to produce urine at each interval. For subjects who are anuric, urine samples for urinalysis will not be collected.

n Subjects will start the confinement on Day -1 and be released from confinement after the 216-hour study assessments (Day 10). Subjects may be required to remain at the CRU for longer at the discretion of the Investigator or designee

º Subjects will be given a stool sample container at screening and instructions on sample collection. They will provide the clinic with a stool sample at their next scheduled visit.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, ConMeds = Concomitant medication,COVID-2019 = Corinavirus disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, eGFR = estimated glomerular filtration rate, ET = early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, MDRD = Modification of Diet in Renal Disease, PK = Pharmacokinetics, PMP = Postmenopausal, RI = Renal Impairment, RR = Respiratory rate, S = Screening, T = Temperature, UA = Urinalysis.

Table 3.a Pharmacokinetic Plasma and Urine Sampling Schedule (Arm 1 and Arm 2)

Study Day	Sample Collection Time	Time (Relative to Dosing) h:min	Plasma Concentrations of Mobocertinib, AP32960, and AP32914	Plasma Protein Binding for Mobocertinib, AP32960, and AP32914	Urine Concentrations of Mobocertinib, AP32960, and AP32914
1	0 h (predose)	00:00 (predose)	✓		✓ (predose void)
	0.5 h	00:30 (±5 min)	✓		✓ 0-12 h [a]
	1 h	01:00 (±10 min)	✓		
	2 h	02:00 (±10 min)	✓	✓	
	4 h	04:00 (±10 min)	✓	✓	
	6 h	06:00 (±20 min)	✓		
	8 h	08:00 (±20 min)	✓		
	12 h	12:00 (±20 min)	✓		
2	0 h	24:00 (±30 min)	✓	✓	✓ 12-24 h [a]
	12 h	36:00 (±30 min)	✓		✓ 24-36 h [a]
3	0 h	48:00 (±30 min)	✓		✓ 36-48 h [a]
4	0 h	72:00 (±60 min)	✓		✓ 48-72 h [a]
5	0 h	96:00 (±60 min)	✓		✓ 72-96 h [a]
6	0 h	120:00 (±60 min)	✓		✓ 96-120 h [a]
8	0 h	168:00 (±60 min)	✓		
10	0 h	216:00 (±60 min)	✓		
Number of samples per subject:			16	3	8

[a] The collection interval will be completed close to nominal time point.

4.0 INTRODUCTION

4.1 Background

Aberrant activation of epidermal growth factor receptor (EGFR) and human epidermal growth factor 2 (HER2) plays a causal role in a subset of non–small cell lung cancer (NSCLC) and other cancers. As inhibition of wild-type (WT) EGFR is associated with dose-limiting toxicities, a tyrosine kinase inhibitor (TKI) that inhibits oncogenic EGFR and HER2 variants more potently than WT EGFR is more likely to be dosed at the more efficacious levels. Multiple classes of activating mutations have been identified in EGFR and HER2 that vary widely in their sensitivity to available TKIs. Mobocertinib, formerly known as AP32788 and TAK-788, was designed to be a potent, selective inhibitor of all activated forms of EGFR and HER2, including exon 20 insertions (not targeted by any approved TKI), more potently than it inhibits WT EGFR.

Non-Clinical Pharmacokinetics

Following oral administration in rats and dogs, urinary and biliary excretions of unchanged drug were negligible (<0.3% and 0.54% - 7.9% respectively). In Sprague-Dawley rats, mobocertinib was eliminated almost completely (97.46% ± 1.70% of the radioactive dose) through feces, and urinary excretion was insignificant (1.98% ± 0.16%). Most of the dose (88.54%) was excreted in 0 to 24 hours. In bile duct-cannulated rats, the average total recovery of administered radioactivity (0-72 hours) was 103.38% ±4.03%, with most of the elimination through bile (57.76% ± 4.19%), indicating that metabolism was the major clearance mechanism.

In vitro studies indicated that the metabolism of mobocertinib was primarily mediated by CYP3A4/5, with minor contributions from CYP2C8, 2C9, 2C19, and 2D6. Systemic exposures to 2 active metabolites, AP32960 and AP32914, accounted for approximately 62% and 9% of parent average concentrations, respectively.

Clinical Pharmacokinetics

The clinical development program for mobocertinib includes an ongoing phase 1/2 clinical efficacy and safety study in patients with NSCLC (AP32788-15-101) and 2 completed clinical pharmacology studies: 1) Single rising dose study (Part 1), low-fat meal effect study (Part 2), and relative bioavailability study (Part 3) in healthy subjects (TAK-788-1001); and 2) a drug-drug interaction (DDI) study to characterize mobocertinib DDI with either a strong cytochrome P-450 (CYP)3A inhibitor, itraconazole (Part 1) or with a strong CYP3A inducer, rifampin (Part 2) in healthy subjects (TAK-788-1006); and 2 ongoing clinical pharmacology studies: TAK-788-1002, and -1004. The objectives and study design of these studies are presented in mobocertinib IB Edition 4 (IB 2020). Only preliminary PK results from AP32788-15-101, and final PK results from TAK-788-1001 and TAK-788-1006 are presented in this document.

In the AP32788-15-101 study, following oral administration of mobocertinib once daily (QD), mobocertinib was readily absorbed with a median time to reach C_{max} concentration (T_{max}) of 4 hours postdose. The single-dose C_{max} and area under the plasma concentration-time curve from

time 0 to 24 hours postdose (AUC_{24}) following multiple doses increased in a less than dose proportional manner across the dose range of 5 to 180 mg.

Minimal to modest mobocertinib accumulation ratios were observed at steady state (geometric mean range 1.23 to 1.52) in the dose range of 20 to 120 mg QD. At 160 mg QD, the geometric mean accumulation ratio following repeated doses was 1.06, suggesting autoinduction of the apparent oral clearance of mobocertinib likely via induction of CYP3A.

The emerging finding of autoinduction by mobocertinib at the 160 mg QD dose is consistent with the results of in vitro induction studies that have shown concentration-dependent CYP3A induction by mobocertinib and its active metabolites, suggesting a possible risk for drug-drug interactions due to induction of CYP3A and other co-regulated enzymes/transporters by mobocertinib as a potential perpetrator. The PK of the 2 active metabolites (AP32960 and AP32914) of mobocertinib were also evaluated in clinical studies. Systemic exposures to metabolites AP32960 and AP32914 in terms of molarAUC_{24} were approximately 62% (%CV: 25%) and 8% (%CV: 13%) of parent AUC_{24} respectively.

In the healthy subject study TAK-788-1001, a low-fat meal (ie, ≤350 calories and ≤15% calories from fat) did not affect the PK of mobocertinib in healthy subjects. At 160 mg mobocertinib, 90% CIs of the GMR with a low-fat meal versus fasted conditions for C_{max} (GMR 0.964) and AUC_{∞} (GMR 0.951) fell completely within 80 -125% range.

In the TAK-788-1006 study, a DDI between the CYP3A4 inhibitor, itraconazole, and mobocertinib was observed. Following coadministration of multiple oral doses of 200 mg itraconazole with a single oral dose of 20 mg mobocertinib, overall (AUC_{∞}) and peak (C_{max}) exposures were increased by approximately 743% and 282% from the corresponding values obtained following mobocertinib alone. Similar results were observed for combined molar AUC_{∞} and combined molar C_{max} data when comparing itraconazole + mobocertinib to mobocertinib alone. A significant reduction in mobocertinib AUC_{∞} and C_{max} was observed when mobocertinib was concomitantly administered with the strong CYP3A4 inducer, rifampin. Following coadministration of multiple oral doses of 600 mg rifampin with a single oral dose of 160 mg mobocertinib, overall (AUC_{∞}) and peak (C_{max}) exposures were reduced by approximately 96% and 95%, respectively, compared to the corresponding values obtained following mobocertinib alone. Similar results were observed for combined molar AUC_{∞} and combined molar C_{max} data when comparing rifampin + mobocertinib to mobocertinib alone.

Refer to the Investigator's Brochure (IB) for detailed background information and safety data on mobocertinib IB Edition 4 (IB 2020).

4.2 Rationale for the Proposed Study

Mobocertinib, formerly known as AP32788 and TAK-788, was designed to be a selective inhibitor of all mutant forms of EGFR and HER2, including exon 20 insertions (not indicated by any approved TKI), and has shown clinically more potent inhibition of these mutant variants than WT EGFR. Mobocertinib is neither a mutagenic nor genotoxic agent and was generally well tolerated in the previous clinical pharmacology studies (TAK-788-1001 and TAK-788-1002, a total of 65 subjects) in healthy subjects in the single dose range of 20–160 mg.

After entering the body, drugs are eliminated by excretion and/or metabolism. Although elimination can occur through a variety of routes, most drugs are cleared by metabolism in the liver and/or small intestine and/or by elimination of unchanged drug by the kidney. Preliminary non-compartmental analysis PK analysis in clinical study with NSCLC patients (AP32788-15-101) shows no effect of baseline mild or moderate RI on the combined molar concentration average (C_{av}) of mobocertinib and its active metabolites, which, together with the minor contribution of renal clearance (<5% of dose as unchanged mobocertinib excreted in urine in healthy subjects) to mobocertinib clearance, supports a reduced design PK study as per Food and Drug Administration (FDA) recommendations (FDA 2020).

The purpose of this PK study (TAK-788-1007) is to assess the PK of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe RI as compared to healthy subjects with normal renal function. These data will be used to provide dose adjustment guidance for cancer patients with severe RI, since this patient population has not been studied in any mobocertinib clinical trials to date.

4.3 Benefit/Risk Profile

The clinical safety data available as of 27 January 2020 indicated no particular safety findings that are unique to mobocertinib compared with other approved EGFR TKIs. The most common treatment-emergent AEs (TEAE) occurring in ≥20% of patients by preferred term overall were diarrhea (84.7%), nausea (45.3%), decreased appetite (31.0%), vomiting (31.0%), fatigue (30.0%), and anemia (23.2%). There is some variety in the characterization of TEAEs of the skin resulting in different PTs to describe it. The most common skin-related PTs were rash (30.5%), dry skin (23.6%), maculo-papular rash (17.2%), paronychia (14.8%), dermatitis acneiform (12.3%), and pruritus (10.8%) (IB 2020).

There will be no direct health benefit for study participants from receipt of study drugs. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

The risk of dosing mobocertinib in subjects with RI is unknown. However, the risk of a single 80 mg dose of mobocertinib administered in this study is anticipated to be similar to those previously reported studies in the mobocertinib IB (IB 2020).The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (ie, 12 lead ECG, vital signs, clinical laboratory tests, AE questioning, and physical examination) are adequate to protect the subject's safety and should detect all TEAEs.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Not applicable

5.2 Study Objectives

5.2.1 Study Primary Objective

To characterize the single-dose plasma and urine PK of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe RI compared to matched-healthy subjects with normal renal function.

5.2.2 Study 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 single oral dose in subjects with severe RI and the matched-healthy subjects with normal renal function.

5.2.3 Study Exploratory Objective

To assess the overall fecal microbiome diversity, serum bacterial antibodies and/or other circulating biomarkers at the baseline.

5.3 Endpoints

5.3.1 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 (bound 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 $AUC_{last,u}$).
- Combined molar unbound $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$ of mobocertinib, AP32960, and AP32914.
- 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.

The following urinary PK parameters will be analyzed for mobocertinib and its active metabolites, such as AP32960 and AP32914:

- Amount of drug excreted in urine from time 0 to time t (Ae_t).
- Fraction of administered dose excreted in urine from time 0 to time t ($f_{e,t}$).
- Renal clearance (CL_R).

5.3.2 Secondary Endpoint

Pharmacokinetics:

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

Safety Endpoints

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

5.3.3 Exploratory Endpoint

Evaluation of baseline microbiome diversity in subjects with impaired renal impairment or subjects with normal renal function.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

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

Table 6.a Study Arms and Planned Dose

Study Arms				
Arm	**Number of Subjects**	**Classification**	**eGRF(a) mL/min**	**Dose**
1	12	Severe	15-29	80 mg
2	12	Matched-Healthy (b)	≥90	80 mg

(a) Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation as defined as follows (for females multiply result by 0.742, if African American multiply result by 1.212):

eGFR = $(175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203})/1.73\ m^2$ (for subjects with standard BSA)

eGFR = $(175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203})$x BSA value $/1.73\ m^2$ (for subjects with non-standard BSA)

$S_{cr, std}$: serum creatinine (mg/dL) measured with a standardized assay.

BSA will be calculated using Dubois and Dubois formula (Dubois and Dubois, 1916)

(b) Healthy subjects with normal renal function will be recruited to match subjects in severe RI arm by age (mean ± 10 years), gender (± 2 subjects per gender), and body mass index (BMI, mean ± 10%).

The study will consist 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.

For assessment of renal function at screening, eGFR will based on the eGFR value calculated by MDRD formula divided by BSA value of 1.73 m^2 for the renal classification category of subjects (ie, severe RI or normal renal function). For subjects with non-standard BSA, the eGFR value calculated by MDRD formula will be multiplied by the individual's BSA calculated using appropriate formula (Dubois and Dubois, 1916) and divide by 1.73 m^2. The eGFR value will be compared to the renal function assignment from historical values within a 6 month period from screening. The subjects to be recruited into this study should show a stable renal function, such as <30% difference in eGFR values, within 6 months from screening. If the renal function of historical and screening assessments falls in the same renal function category with <30% difference, the subject can be enrolled into this study if other inclusion criteria are met and none of the exclusion criteria are met. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (at least 72 hours apart) and the two values have to show <30% difference and fall in the same renal function category of either severe RI or normal renal function before check-in. If the results of the 2 most recent assessments are not in agreement with regard to the subject's renal function category, the third assessment has to be performed at least 72 hours after the second assessment. If the second and third measurements differ, the subject will not be eligible for the study.

Subjects will receive a single oral dose of 80 mg mobocertinib capsule on Day 1 (Table 6.b).

Table 6.b Study Design for Arms 1 and 2

Study Day	S	-1	1	2	3	4	5	6	8	10
Mobocertinib PO (80 mg)			X							
PK Blood Samples			X	X	X	X	X	X	X	X
PK Urine Samples			X	X	X	X	X	X		
Blood Sample for Bacterial Antibodies and Other Circulating Biomarkers	X									
Stool Sample for Microbiome Research	X									
Confinement in CRU		X	X	X	X	X	X	X	X	X

CRU-clinical research unit; PK-pharmacokinetic; PO-per os (by mouth); S-screening.

Blood samples will be collected from Days 1 to 10 and urine PK samples will be collected from Day 1 to the morning of Day 6 at predetermined time points to characterize the plasma and urine PK and plasma protein binding of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe RI and in matched-healthy subjects with normal renal function.

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

Subjects will be confined in the CRU from Day -1 until the morning of Day 10 after the 216-hour study assessments are complete. A subject may be required to remain at the CRU for longer periods, at the discretion of the Investigator. Subjects may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per CRU requirements.

A final safety follow up phone call will occur 30 ± 2 days after mobocertinib dosing to determine if any AEs have occurred since last study visit.

6.2 Dose Escalation

There will be no dose modifications for this study.

6.3 Rationale for Study Design, Dose, and Endpoints

6.3.1 Rationale of Study Design

According to the FDA Draft Guidance March 2020 – Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing (FDA 2020), a "reduced pharmacokinetic study" may be used for drugs which are predominantly eliminated via nonrenal routes. If no substantial difference (eg, AUC increase of <50%) in pharmacokinetics is seen between subjects with severe renal impairment as compared to healthy subjects, no further study needs to be undertaken. The severe renal impairment group has been chosen based on the classification system within the aforementioned Draft Guidance.

As per the FDA guidance, a healthy subject control group will be enrolled with demographics which are reasonably matched to the mean demographic parameters to control for the influence of covariates in PK assessment. In the current study the covariates of BMI, age and gender will be matched. Following the categorization of renal function outlined in the Draft Guidance, healthy subjects will have an eGFR ≥90 mL/min and severely impaired subjects will have an eGFR 15-29 mL/min (FDA 2020).

6.3.2 Rationale for Dose

The dose selected for this study with severe renal impairment is 80 mg of mobocertinib taken orally; this corresponds to 50% of the highest single oral dose evaluated in healthy subjects (ie, 160 mg) and will provide a safety margin. In the event that renal impairment delays drug clearance and increases overall systemic exposure, it is anticipated that a single oral dose 80 mg administered to patients with severe renal impairment will not exceed the historical exposure levels seen in healthy subjects of a single oral dose of 160 mg dose of mobocertinib.

6.3.3 Rationale for Endpoints

6.3.3.1 Pharmacokinetic Endpoints

Given that mobocertinib, AP32960, and AP32914 are pharmacologically active, with similar in-vitro potency to inhibit EGFR/HER2 exon 20 insertions, the statistical analyses of PK exposure parameters will be performed on the molecularly weight adjusted combined exposure of mobocertinib and its active metabolites along with the exposure parameters of mobocertinib, AP32960, and AP32914 individually.

Renal impairment can adversely affect some pathways of hepatic/gut metabolism that might lead to changes to plasma protein binding (FDA 2020). Since mobocertinib and its active metabolites display high binding to plasma proteins in vitro, renal impairment may affect plasma protein binding of mobocertinib and its active metabolites. Therefore, the statistical analyses of PK exposure parameters will be conducted using the unbound PK parameters.

6.3.3.2 Safety Endpoints

The key safety endpoints are typical for phase 1 studies and will be assessed through monitoring of adverse events, vital signs, ECGs, laboratory assessments and physical examinations

6.3.4 Future Biomedical Research

Any residual plasma samples will be stored by the Sponsor or Bioanalytical facility for the maximal 5 years determined by Sponsor following dosing and may be used in the future to perform metabolite profiling. Tubes or container will be identified with a barcode using an appropriate label.

No diseases/conditions, deoxyribonucleic acid, or ribonucleic acid will be the focus of these analyses. The analyses will focus on metabolite profiling for mobocertinib compound. Samples will not be submitted to a public database. The Sponsor and contract research organizations

involved in the clinical conduct, bioanalytical analyses and PK and statistical analysis of the data will have access to the samples and/or the data that resulted from the analysis, if performed.

By signing the ICF, subjects agree to the possible future analysis of these samples. At any time, the subjects can contact the CRU staff to request destruction of the residual samples once PK assessments required to meet the primary objective of the study are completed. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

6.3.5 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the critical component is the blood collection for plasma concentrations of mobocertinib and its active metabolites (AP32960 and AP32914) and samples are required to be collected, as appropriate, as close to the scheduled times defined in this protocol as possible.

6.4 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of the study drugs to any subject may not be modified. If necessary, a subject may be discontinued for the reasons described in Section 7.5 and Section 7.6.

6.5 Study Beginning and End/Completion

6.5.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (ie, signing of the ICF) of the first subject.

6.5.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3.0).

6.5.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in the follow-up phone call for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subject is lost to follow-up.

6.5.4 Definition of Study Discontinuation

Celerion and/or the clinical site reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.5.5 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.5.6 Criteria for Premature Termination or Suspension of a Site

There is no predetermined criteria for termination of suspension of a site.

Termination or suspension of a site may occur at any time at the discretion of the Sponsor.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

7.1.1 Inclusion Criteria for Healthy Subjects

All healthy subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult male or female subjects aged ≥18 to <81 years, at screening. Subjects will be matched to RI subjects by age (mean ± 10 years) at screening.
2. Continuous non-smoker or moderate smoker (≤10 cigarettes/day or the equivalent) before screening. Subject must agree to consume no more than 5 cigarettes or equivalent/day from the 7 days prior to mobocertinib dosing and throughout the period of PK sample collection.
3. BMI ≥18.0 and ≤39.0 kg/m^2, at screening. Subjects will be matched to RI subjects by BMI (mean ± 10 %) at screening. At least 50% of the subjects will be required to be of BMI ≥18.0 and ≤35.0 kg/m^2, at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee. Has liver function tests including ALT, AST, ALP, and total bilirubin within the upper limit of normal at screening and at check-in.
5. Baseline eGFR ≥90 mL/min/1.73m^2 based on the MDRD equation at screening divided by standard BSA value of 1.73 m^2. For subjects with non-standard BSA, the eGFR value calculated by MDRD formula will be multiplied by the individual's BSA calculated using appropriate formula and divided by 1.73 m^2.
6. Female subjects of nonchildbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing:

- hysteroscopic sterilization;
- bilateral tubal ligation or bilateral salpingectomy;
- hysterectomy;
- bilateral oophorectomy;

or be postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status.

7. Female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 30 days following the mobocertinib dosing as indicated in Appendix D.
8. Female subjects must agree not to donate ova/oocytes during the study and for at least 30 days following mobocertinib dosing as indicated in Appendix D.
9. Males subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in Appendix D or abstain from sexual intercourse during the study until at least 30 days following mobocertinib dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with his preferred and usual lifestyle.
10. Male subjects must agree not to donate sperm from dosing until at least 30 days following mobocertinib dosing as indicated in Appendix D.
11. Understands the study procedures in the ICF and be willing and able to comply with the protocol.

7.1.2 Inclusion Criteria for Subjects with Renal Impairment

All RI subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Adult male or female subjects aged ≥18 to <81 years, at screening.
2. Continuous non-smoker or moderate smoker (≤10 cigarettes/day or the equivalent) before screening. Subject must agree to consume no more than 5 cigarettes or equivalent/day from the 7 days prior to dose of mobocertinib and throughout the period of PK sample collection.
3. BMI ≥18.0 and ≤39.0 kg/m^2, at screening. At least 50% of the subjects will be required to be of BMI ≥18.0 and ≤35.0 kg/m^2, at screening.
4. Aside from RI, be sufficiently healthy for study participation based upon medical history, physical examination, vital signs, ECGs, and screening clinical laboratory profiles, as deemed by the Investigator or designee.
5. Baseline eGFR 15-29 mL/min not on dialysis based on the MDRD equation at screening divided by standard BSA value of 1.73 m^2. For subjects with non-standard BSA, the eGFR

value calculated by MDRD formula will be multiplied by the individual's BSA calculated using appropriate formula and divided by 1.73 m^2.

6. Has a diagnosis of chronic (>6 months), stable (no significant changes in renal function [<30%] in the 30 days preceding screening; no acute episodes of illness within the previous 2 months due to deterioration in renal function) renal insufficiency. Subjects with RI may have related medical conditions consistent with their disease (eg, mild diabetes) that are stable for at least 3 months prior to screening, in the opinion of the Investigator or designee.
7. For a female of nonchildbearing potential, must have undergone one of the following sterilization procedures at least 6 months prior to dosing:
   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status.
8. Female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 30 days following mobocertinib dosing as indicated in Appendix D.
9. Female subjects must agree not to donate ova/oocytes during the study and for at least 30 days following mobocertinib dosing as indicated in Appendix D.
10. Males subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in Appendix D or abstain from sexual intercourse during the study until at least 30 days following mobocertinib dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with his preferred and usual lifestyle.
11. Male subjects must agree not to donate sperm from dosing until at least 30 days following mobocertinib dosing as indicated in Appendix D.
12. Understands the study procedures in the ICF and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

7.2.1 Exclusion Criteria for Healthy Subjects

All healthy subjects must be excluded from participating in the study if the subject:

1. Mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subjects by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
5. History or presence of clinically significant hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. History or presence of any previous significant lung disease except child asthma.
7. History of lung infection, within 3 months of screening or ongoing lung infection.
8. Female subjects with a positive pregnancy test or who are lactating.
9. Positive results for urine or breath alcohol screen at screening or check-in.
10. Positive results for urine or saliva drug screen at screening or check-in unless the positive drug screen is due to prescription drug use that is approved by the Investigator and Sponsor.
11. Positive results at screening for HIV, HBsAg, or HCV.
12. Positive test result for COVID-19 testing at screening or check-in.
13. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
14. Seated blood pressure is less than 90/40 mmHg or greater than 150/95 mmHg at screening.
15. QTcF interval is ≥450 msec in males or ≥470 msec in females or has ECG findings deemed abnormal with clinical significance by the Investigator or designee at screening.
16. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 7.3 (Prohibitions and Concomitant Medication) for the prohibited time period.
17. Been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to dosing and throughout the study.
18. Donation of blood or significant blood loss within 56 days prior to dosing.
19. Plasma donation within 7 days prior to dosing.
20. Participation in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.

7.2.2 Exclusion Criteria for Subjects with Renal Impairment

All RI subjects must be excluded from participating in the study if the subject:

1. Mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical, aside from RI, or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subjects by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
5. History or presence of clinically significant hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. History or presence of any previous significant lung disease except child asthma.
7. History of lung infection, within 3 months of screening or ongoing lung infection.
8. Fluctuating or rapidly deteriorating renal function within the screening period, and up to 30 days prior to Day 1, in the opinion of the Investigator and Sponsor.
9. Failed renal transplant or has had nephrectomy.
10. Rapidly fluctuating renal function, as determined by historical measurements; or has demonstrated or suspected renal artery stenosis. Rapidly fluctuating renal function is defined as eGFR that differs by more than 30% within a 6 month period before the screening. If historical measurements are not available, then the 2 screening measurements will be used to demonstrate stability; a second baseline eGFR sample will be taken during the screening period (at least 72 hours apart) and the two values have to show <30% difference and fall in the same renal function category of either severe RI or normal renal function before check-in. If the results of the 2 most recent assessments are not in agreement with regard to the subject's renal function category, the third assessment has to be performed at least 72 hours after the second assessment. If the second and third measurements differ, the subject will not be eligible for the study.
11. Female subjects with a positive pregnancy test or who are lactating.
12. Positive results for urine or breath alcohol screen at screening or check in.
13. Positive results for urine or saliva drug screen at screening or check in unless the positive drug screen is due to prescription drug use that is approved by the Investigator and Sponsor.
14. Positive results at screening for HIV, HBsAg, or HCV.
15. Positive test result for COVID-19 testing at screening or check-in.
16. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
17. Seated blood pressure is less than 90/40 mmHg or greater than 180/100 mmHg at screening.
18. QTcF interval is >500 msec or has ECG findings deemed abnormal with clinical significance by the Investigator or designee at screening.
19. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as

indicated in Section 7.3 (Prohibitions and Concomitant Medication) for the prohibited time period.

20. Been on a diet incompatible with the on study diet, in the opinion of the Investigator or designee, within the 30 days prior to dosing and throughout the study.
21. Donation of blood or significant blood loss within 56 days prior to dosing.
22. Plasma donation within 7 days prior to dosing.
23. Participation in another clinical study within 30 days prior to dosing. The 30 day window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.

7.3 Prior and Concomitant Medications and Therapies

Concomitant therapies include any therapies, over-the-counter medications, herbal products, vitamin and/or mineral supplements used by a subject from Day 1 through Day 10. A record of all medications used will be maintained for each subject throughout the study. Reported information will include a description of the type of drug, treatment period, dosing regimen, the route of administration, and drug indication.

Subjects will be instructed to inform the study Investigator of the details (indication, dose and dates of administration) if they take any medication prior to clinic check-in, and these details will be recorded in the CRF.

Healthy subjects will be restricted of using any prescription medications/products and any over-the-counter, nonprescription preparations (including herbal products, natural or herbal supplements) from at least 14 days before dosing and throughout the study. However, healthy subjects that are on stable medication for at least 30 days prior to dosing may be enrolled upon approval by the Investigator (or designee) and Sponsor.

Subjects with RI who are taking medications to treat manifestations of renal disease or medications needed to treat for stable diseases (eg, diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and beta-blockers) will be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor. For renal disease related medical conditions, subjects must be on a stable dose (steady dose, drug, and regimen) for at least 14 days and able to withhold the use for at least 4 hours post-dose. Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations; H2-receptor antagonists (H2RAs [except cimetidine]); or multivitamins containing iron or zinc must be withheld at least 8 hours before dosing and at least 6 hours postdose.

Any medication (including over-the-counter) that would significantly alter CLcr values which, by the determination of the Investigator and the Sponsor, might interfere with the study (eg, cimetidine) must be discontinued at least 14 days (or 5 half-lives of the compound, whichever is longer) prior to dosing.

If a subject with RI is prescribed prohibited medication, upon discussion between the Sponsor and the Investigator, the Investigator may substitute the previously prescribed medication to an allowed one for the purpose of this study.

For all subjects, any drugs known to be strong or moderate inhibitors of CYP3A enzymes and/or P-gp will be restricted for 14 days, and any drugs known to be strong or moderate inducers of CYP3A enzymes and/or P-gp, including St. John's Wort, will be restricted for 28 days, before dosing and throughout the study. Use of weak inhibitors or inducers may be deemed acceptable following consultation with the Sponsor and the Investigator or designee. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with study drug.

For all subjects, following dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to dosing.

All medications taken by subjects during the course of the study will be recorded.

Concurrent medication during the course of the study including both prescription and nonprescription drugs may be permitted based on the timing of study drug administration and its pharmacology, but must first be discussed with the Investigator or designee and Sponsor prior to dosing, unless appropriate medical care necessitates that therapy should begin before the Investigator or designee and Sponsor can be consulted.

7.4 Excluded Medications, Supplements, Dietary Products

Use of excluded agents (prescription or nonprescription) or dietary products is outlined in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and Dosing (Days -14 to predose [Day 1])	After Dosing (Day 1) through Follow-up
Alcohol	Prohibited from 48 hours prior to dosing	Prohibited up to Day 10, inclusively.
Xanthine and/or caffeine	Prohibited from 24 hours prior to dosing [a]	Prohibited up to Day 10, inclusively [a].
Medications	See Sections 7.2 and 7.3	See Sections 7.2 and 7.3
Food substance		
Grapefruit/Seville orange	Prohibited from 28 days prior to dosing	Prohibited up to Day 10, inclusively

[a] small amounts of caffeine derived from normal foodstuffs eg, 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction.

If deviations occur, the Investigator will decide on a case-by-case basis whether the subject may continue participation in the study based on the time the drugs were administered and their pharmacology.

7.5 Diet, Fluid, Activity

7.5.1 Diet and Fluid

Water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after study drug administration, but will be allowed *ad libitum* at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

On Day 1, subjects will fast overnight for at least 10 hours prior to oral study drug administration and will continue to fast for at least 4 hours postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks. Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition.

7.5.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose on Day 1, except when they are supine or semi-reclined for study procedures or AEs.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

Depending on the CRU rules and regulations, subjects may be prohibited from smoking during their confinement or during portions of their confinement.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the Investigator or designee for the following reasons:

- AEs.
- A positive pregnancy test for females.
- Positive urine or saliva drug or alcohol results.
- Difficulties in blood collection.

A subject may be withdrawn by the Investigator (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by

the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.8 Subject Replacement

Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis by the Sponsor and Investigator to ensure approximately 12 PK-evaluable subjects complete in each arm of study.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

8.1.1 Mobocertinib Capsules

A single dose of 80 mg mobocertinib (2 x 40 mg mobocertinib capsules) will be administered on Day 1.

Mobocertinib drug product is a nonsterile, oral, capsule dosage form. Mobocertinib succinate salt is the active pharmaceutical ingredient encapsulated in a hard gelatin capsule shell with no excipients.

Mobocertinib (AP32788) 40 mg: Size 1, white, opaque, hard gelatin capsules 30 capsules per bottle

8.1.2 Clinical Study Drug Labeling

Mobocertinib capsule containers will be affixed with a clinical label in accordance with local regulatory requirements.

The pharmacy at the CRU will provide the in individual unit dose containers for each subject.

8.1.3 Clinical Study Drug Inventory and Storage

Mobocertinib capsules

The Sponsor will supply sufficient quantities of mobocertinib products to allow completion of this study.

- Store below 30°C (86°F).
- Do not refrigerate or freeze – Normal room temperature.
- Keep away from cold or heat sources.
- Keep out of reach and sight of children.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

8.1.4 Clinical Study Drug Blinding

This is an open-label study.

8.1.5 Randomization Code Creation and Storage

Not applicable

8.1.6 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable

8.1.7 Accountability and Destruction of Sponsor-Supplied Drugs

At the conclusion of the study, any unused mobocertinib study drug will be retained by CRU, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 13.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

9.1.1.1 Assignment of Screening and Allocation Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of dosing, different from the screening number.

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

9.1.1.2 Study Drug Assignment

All subjects will receive mobocertinib as detailed in Section 8.1.

9.1.2 Inclusion and Exclusion

Subjects must satisfy all of the inclusion criteria and meet none of the exclusion criteria as outlined in Sections 7.1 and 7.2, respectively in their applicable study arm.

9.1.3 Medical History/Demography

Medical history and demographic data, including subject number sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be permitted or prohibited as listed in Sections 7.2 and 7.3. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to subject safety.

For this study, the collection of blood for mobocertinib PK is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time (refer to Table 3.a).

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.2.1 Full Physical Exam

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a seated position (subjects must be seated for at least 5 minutes prior to measurement), except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.

Blood pressure and heart rate will be measured within 24 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

ECGs will be performed with subjects in a supine position. Subjects are required to be supine for at least 5 minutes prior to the ECG measurement. All ECG tracings will be reviewed by the Investigator or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Pulmonary Function Test

9.2.6.1 Spirometry

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

9.2.7 Study Drug Administration

Mobocertinib oral capsules will be provided as described in Section 8.0.

Subjects will be instructed not to crush, split, or chew the mobocertinib capsules.

Mobocertinib will be administered following an overnight fast.

Mobocertinib will be administered with approximately 240 mL of water. The exact clock time of oral dosing will be recorded.

The pharmacy at the CRU will provide study drug in individual unit dose containers for each subject as appropriate.

9.2.8 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 10.0.

9.2.9 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample is taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Amylase	Albumin
Lipase	Sodium
Blood Urea Nitrogen	Potassium
Bilirubin (total and direct)	Chloride
Alkaline phosphatase	Glucose
Aspartate aminotransferase	Creatinine *
Alanine aminotransferase	Magnesium

* At screening, eGRF will be calculated based on MDRD for renal classification assignment.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine or saliva drug screen – Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone) – Amphetamines – Barbiturates – Benzodiazepines – Cocaine – Cannabinoids
HBsAg	
HCV	
Urine or breath alcohol screen	
Serum pregnancy test (for females only)	
FSH (for postmenopausal females only)	
Blood and fecal samples for microbiome research	
COVID-19 testing (performed according to CRU standard procedures detailed in a separate document[s])	

9.3 Pharmacokinetic Samples

Instructions for plasma and urine samples processing and handling will be provided in a separate document.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Plasma sample for mobocertinib and metabolites PK	Plasma	Plasma sample for mobocertinib and metabolites PK analysis	Mandatory
Plasma sample for mobocertinib and metabolites protein binding	Plasma	Plasma sample for mobocertinib and metabolites protein binding	Mandatory
Urine sample for mobocertinib and metabolites PK	Urine	Urine sample for mobocertinib and metabolites PK analysis	Mandatory
Stool sample for microbiome assessment	Feces	Fecal microbiome diversity at the baseline	Mandatory
Serum sample for bacterial antibodies and other circulating biomarkers	Serum	Serum for bacterial antibodies and other circulating biomarkers at baseline	Mandatory

9.3.1 PK Measurements

9.3.1.1 Plasma PK Measurements

Total and unbound plasma PK parameters for mobocertinib and metabolites AP32960 and AP32914 will be calculated as follows, as appropriate, following oral administration:

AUC_{last}:	The area under the concentration versus time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method for total analyte.
$AUC_{last,u}$:	The area under the concentration versus time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method for unbound analyte.
AUC_{∞}:	The area under the concentration versus time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_{last} plus the ratio of the last measurable blood concentration to the elimination rate constant for total analyte.
$AUC_{\infty,u}$:	The area under the concentration versus time curve, from time 0 extrapolated to infinity. AUC_u is calculated as AUC_{ulast} plus the ratio of the last measurable blood concentration to the elimination rate constant for unbound analyte.
$AUC_{\%extrap}$:	Percent of AUC_{∞} extrapolated, represented as $(1 - AUC_{last}/AUC_{\infty})*100$.
CL/F	Apparent total plasma clearance after oral (extravascular) administration, calculated as $Dose/AUC_{\infty}$ (mobocertinib only).
CL_u/F	Apparent total plasma clearance after oral (extravascular) administration, calculated as $Dose/AUC_u$ (mobocertinib only).
C_{max}:	Maximum observed concentration for total analyte.
$C_{max,u}$:	Maximum observed concentration for unbound analyte.
t_{max}:	Time to reach C_{max}. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
$t_{½z}$:	Apparent first-order terminal elimination half-life will be calculated as $0.693/\lambda_z$. Where λ_z is the apparent first order terminal elimination rate constant calculated from a semilog plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares- regression analysis using the maximum number of points in the terminal log-linear phase (eg, three or more non-zero plasma concentrations).

V_z/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as Dose/(AUC_∞ x λ_z) (mobocertinib only).
$V_{z,u}/F$	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as Dose/(AUC_u x λ_z) (mobocertinib only).

No value for λ_z, AUC_∞, $AUC_{\infty,u}$, $AUC_{\%extrap}$, CL/F, CL_u/F, V_z/F, $V_{z,u}/F$, or $t_{½z}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for subjects with detectable concentrations at 2 or fewer consecutive time points.

Individual and mean plasma concentration-curves (both linear and log-linear) will be included in the final report.

9.3.1.2 Urine PK Measurements

PK parameters for urine mobocertinib and metabolites AP32960 and AP32914 concentrations will be calculated as follows, as appropriate, following oral administration:

Ae_t:	Total amount of drug excreted unchanged in the urine from time 0 to the last observed non-zero concentration, obtained by adding the amounts excreted over each collection interval.
$f_{e,t}$:	Fraction administered dose excreted in urine from time 0 to time t.
CL_R:	Renal clearance calculated as $Ae_{(t'-t")}/AUC_{(t'-t")}$ where t'-t" is the longest interval of time during which Ae and AUC are both obtained.

9.3.2 Microbiome Assessment

A baseline stool samples per subject will be collected for the evaluation of microbiome using 16S rRNA (ribosomal ribonucleic acid) sequencing and/or DNA sequencing for metagenomics as indicated in the Section 3.0.

A blood sample for serum bacterial antibodies and/or other circulating biomarkers will be obtained as indicated in the Section 3.0.

9.3.3 PGx Measurements

Not applicable

9.3.4 Confinement

Subjects will be housed on Day -1, at the time indicated by the CRU, until the morning of Day 10 after the 216-hour PK sample is collected and study procedures are complete, as indicated in

Section 3.0. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the Investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, Investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after administration of study medication or after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1.1 and 10.2.6.3).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

There are no AEs of Special Interest for this study.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, dated 27 November 2017 [CTCAE 2017]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on subject/event outcome or action criteria described above and is usually associated with events that pose a threat to a subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to <2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or Investigator.

10.2.4 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.5 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.

- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.6 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.6.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up phone call 30 days (± 2 days) after mobocertinib dosing. For subjects who discontinue prior to the administration of mobocertinib, AEs will be followed until the subject discontinues study participation.

10.2.6.2 Reporting AEs

At follow-up, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious AEs that begin prior to exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with Study drug.
- Outcome of event.
- Seriousness.

10.2.6.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.6.4 Reporting Special Interest AEs

Not applicable

10.2.6.5 Reporting of Abnormal Liver Function Tests

If a subject has elevated ALT ≥3x upper limit of normal (ULN) with concurrent elevated total bilirubin >2x ULN ***or*** elevated international normalized ratio (INR) >1.5, contact the sponsor's medical monitor within 24 hours.

For any subject with ALT ≥3x ULN and total bilirubin >2 x ULN or INR >1.5x ULN for which an alternative etiology has not been found, report the event as an SAE (Section 10.2.6.3) and contact the sponsor immediately.

10.2.7 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the Study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.2.8 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses provided below.

Product	Call Center	Phone Number	Email	Fax
Mobocertinib	Dohmen Life Science Services, or DLSS (formerly known as MedComm)	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo @takeda.com	1-800-881-6092

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also

be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 Pharmacokinetic 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 and display an evaluable PK profile (eg, exposure to treatment, availability of 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 will be excluded in the final data analysis.

11.1.1.2 Safety Set

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

11.1.1.3 Pharmacodynamic Set

Not applicable.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, gender, race, and ethnicity) will also be listed and tabulated.

11.1.3 Pharmacokinetic Analysis

PK parameters for plasma concentrations of mobocertinib and metabolites (AP32960 and AP32914) will be calculated as described in Section 9.3.1.1, and outlined in the SAP.

The ln-transformed of the combined molar unbound $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$ for mobocertinib and its metabolites (AP32960 and AP32914) will be compared between renal impairment and the healthy arms using an ANOVA model. The ANOVA model will include renal impairment versus normal conditions as a fixed effect and subject nested within group as a random effect. Each ANOVA analysis will calculate the LSM, the difference between group LSMs, and the standard error associated with the difference. Residual, subject nested within group, and intersubject variance will be reported. Ratio of LSM and 90% CI will be calculated using the exponential function of the difference between group LSMs from the analysis on the ln-transformed combined molar unbound $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$ of mobocertinib, AP32960, and AP32914.

The same analysis will be repeated for each analyte (mobocertinib, AP32960, and AP32914) separately and will be performed on total PK parameters as well (C_{max}, AUC_{last}, and AUC_{∞}).

11.1.4 Pharmacodynamic Analysis

Not applicable.

11.1.5 Safety Analysis

All safety data will be populated in the individual CRFs.

Dosing dates and times will be listed by subject.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.5.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by population for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

11.1.5.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by population and point of time of collection and a shift table describing out of normal range shifts will be provided.

11.1.5.3 Vital Signs

Vital signs assessments will be summarized by population and point of time of collection.

11.1.5.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs will be summarized by population and point of time of collection.

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization drug dictionary and will be listed by subject.

11.2 Interim Analysis and Criteria for Early Termination

There are no interim analysis in this study.

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

11.3 Determination of Sample Size

The planned sample size of 12 subjects in each renal function arm is considered adequate to provide a precise estimation of the combined molar AUC_∞ of mobocertinib and its active metabolites AP32960, and AP32914 in subjects with severe renal impairment compared to healthy subjects with normal renal function. The sample size calculation was based on the 95% confidence interval (CI) for the geometric mean of the combined molar AUC_∞ of mobocertinib and its active metabolites AP32960, and AP32914. The average interpatient coefficient of variation for mobocertinib, AP32960, and AP32914 apparent clearance was estimated to be [redacted]

[redacted] With a sample size of 12 in each renal function arm, the 95% CI for the for the geometric mean of the combined molar AUC_{∞} is expected to be 0.6 to 1.4 with at least 80% power according to the variance assumptions.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The Investigator and study site guarantee access to source documents by the Sponsor or its designee (Clinical Research Organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of CRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to Study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each Investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the Study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and Sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and, if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

13.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (eg, subject name, address, and other identifier fields not collected on the subject's CRF).

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During and after the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study Registration

In order to ensure that information on clinical studies reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical studies it Sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with Investigator's city, state (for Americas Investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the Investigator name, address, and phone number to the callers requesting Study information. Once subjects receive Investigator contact information, they may call the site requesting enrollment into the Study. The investigative sites are encouraged to handle the Study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of Study enrollment, they should be referred to the Sponsor.

Any Investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

Takeda will post the results of clinical studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the Sponsor's policy on subject compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	**SAE Reporting Contact Information** **Cognizant** **US and Canada** Toll-free fax #: 1-800-963-6290 E-mail: takedaoncocases@cognizant.com

Please refer to Safety Management Plan.

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 [R2] Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.7 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

_____
Signature of Investigator Date

_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State/Provence)

_____
Location of Facility (Country)

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{last}	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration total
$AUC_{last,u}$	Area under the concentration-time curve from time 0 to time t the last observed non-zero concentration unbound
AUC_{∞}	Area under the concentration-time curve, from time 0 extrapolated to infinity total
$AUC_{\infty,u}$	Area under the concentration-time curve, from time 0 extrapolated to infinity unbound
BMI	Body mass index
bpm	Beats per minute
C_{av}	Average concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent clearance after extravascular administration total
CL_u/F	Apparent clearance after extravascular administration unbound
cm	Centimeter
C_{max}	Maximum observed concentration, total
$C_{max,u}$	Maximum observed concentration, unbound
COVID-19	Corona virus disease 2019
CRA	Clinical Research Associate
CRF	Case report form
CRU	Clinical Research Unit
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HER2	Human epidermal growth factor 2
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	Kilogram
LFT	Liver function test
LSM	Least-squares mean
m^2	Meters squared
MDRD	Modification of Diet in Renal Disease
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NSCLC	Non–small cell lung cancer
P-gp	P-glycoprotein
PFT	Pulmonary function test
PK	Pharmacokinetic(s)
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RI	Renal impairment
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
$t_{½z}$	Apparent first-order terminal elimination half-life
t_{max}	Time to reach C_{max}
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
US	United States
USA	United States of America
V_z/F	Apparent volume of distribution after extravascular administration total
$V_{z,u}/F$	Apparent volume of distribution after extravascular administration unbound
WT	Wild-type
λ_z	Apparent first order terminal elimination rate constant

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan.

15.1 CRFs

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor or its designee will train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. CRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal Investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the Investigator/designee with use of change and modification records of the CRFs. The Principal Investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

15.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 [R2] Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6

[R2] (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 [R2] Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The Investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

1. Dubois D, Dubois EF, 1916, A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, Arch Intern Med, 17:863-871.
2. National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Revised: Nov-2017 (v5.0). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.
3. Mobocertinib. Millennium Pharmaceuticals, Inc. Global Investigator Brochure. Edition 4.0, 01 April 2020.
4. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Draft Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function —Study Design, Data Analysis, and Impact on Dosing. September 2020.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the Investigator may participate in this study.

The Investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the Investigator/institution retains the services of any individual or party to perform Study-related duties and functions, the Investigator/institution should ensure that this individual or party is qualified to perform those Study-related duties and functions and should implement procedures to ensure the integrity of the Study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s).
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for at least 30 days after the dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the Investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for at least 30 days after the dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the Investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical Study information from this Study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of Investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting Investigator site contact information, study details and results on publicly accessible clinical Study registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in Investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Mobocertinib may pose a risk to developing fetuses or to babies who are being breastfed. Because mobocertinib may affect an unborn baby, female participants should not become pregnant while in this study, and male participants should not conceive with their female partner(s) while in this study. Women who are pregnant or breastfeeding will not be allowed to take part in this study.

Women of childbearing potential and male subjects must use medically acceptable birth control. Avoiding sexual activity is the only certain way to prevent pregnancy.

Males Subjects and Their Female Partners:

It is not known whether the study medication will affect sperm or an unborn baby. Based on animal studies, taking mobocertinib may lead to testicular changes that could impact reproduction. For this reason, to be in the study males must agree not to father a child or donate sperm during the study and for at least 30 days after mobocertinib dosing.

If a male has not had a vasectomy and is sexually active with any person who is pregnant, or could get pregnant, he must use a condom with spermicidal cream or jelly each time he has sex during the study and for at least 30 days after mobocertinib dosing. If a male is surgically sterilized (ie, have had a vasectomy) he must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) during the entire study, and for at least 30 days after his mobocertinib dosing. Or, he should completely avoid having heterosexual intercourse.

If a female partner does become pregnant while a male subject is taking part in the study, the subject must tell the study doctor immediately.

In this situation, the female partner should be under medical supervision during her pregnancy, and the baby should be under supervision after it is born. The female partner may be asked to give her consent to the collection of information related to both herself as well as the baby.

Acceptable birth control for males with female partners includes any of the following:

- total abstinence (no sexual intercourse) if it agrees with his preferred and usual lifestyle.
- a barrier method (latex condom with a spermicidal agent).

Males must use acceptable birth control during the study treatment period and for at least 30 days after mobocertinib dosing and should tell their female partner(s) that they are in research study.

Females:

Females must agree not to become pregnant, breastfeed a baby or donate an egg or eggs (ova) during the study and for at least 30 days after mobocertinib dosing. Women of childbearing potential must use acceptable birth control from the time of signing the informed consent form until at least 30 days after their mobocertinib dosing.

If a female has been surgically sterilized or is postmenopausal, she does not need to meet any contraception requirements to take part in this study.

If a female is of childbearing potential and is sexually active with a male partner, she must be willing to use an acceptable method of contraception during the study and for at least 30 days after mobocertinib dosing.

Mobocertinib may decrease effectiveness of hormonal contraceptives, therefore, women must use an effective non-hormonal methods of contraception. Acceptable birth control for women of childbearing potential with male partners must include one form of highly effective non-hormonal contraception and one additional effective (barrier) method, as described below:

Highly effective non-hormonal methods	**Additional effective (barrier) methods**
Nonhormonal intrauterine device	Male or female condom with or without spermicide (female and male condoms should not be used together)
Vasectomised sole sexual partner (removal of the tube that carries sperm from the testicle to the penis)	
Sexual abstinence (no sexual intercourse)	Cap, diaphragm or sponge with spermicide

Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with her preferred and usual lifestyle.

In order to enter the study, all females must have a pregnancy test to confirm that she is not pregnant. This test will be repeated just before she starts taking study medication at check-in. If a pregnancy test during the study shows that she may be pregnant, she will be withdrawn from the study and the treatment will end. She will be asked for the results of any tests and procedures carried out during pregnancy and up to the birth. She may also be asked for the results from any evaluation of the baby after the birth.

Appendix E Detailed Description of Amendments to Text: Amendment 1

Change 1. Due to the COVID-19 pandemic of 2020, the mandatory measurement of the PFT was removed from the protocol to diminish the risk of airborne virus transmission during the study conduct.

The following sections were updated to reflect this change:

- Removal of Inclusion criteria 6 for healthy subjects and 7 for subjects with RI, and the indication in the study design in Section 1.0 – Study Summary,
- Change in the PFT associated footnote "j" in Section 3.0 – Schedule of Study Procedures,
- Removal of the PFT in Section 4.3 – Benefit/Risk Profile,
- Removal of criterion 6 in Section 7.1.1**.** – Inclusion Criteria for Healthy Subjects, removal of criterion 7 in Section 7.1.2- Inclusion Criteria for Subjects with Renal Impairment
- Removal of details of the PFT in Section 9.2.6 – Pulmonary Function Test
- Removal of abbreviations FEV1 and FVC in Section 14.1.4 – List of Abbreviations.

Removed Wording:	Pulmonary Function Test (PFT) (spirometry) is required to be performed and be assessed as normal at screening. Post-dose PFTs will be performed only if indicated on the basis of pulmonary symptoms at the discretion of the Investigator or designee (Section 1.0 and Section 6.0). Inclusion criteria 6 (Section 1.0 and Section 7.1.1) and 7 (Section 1.0 and Section 7.1.2): Normal baseline spirometry for FVC and FEV1/FVC within 7 days prior to dosing based on the following normal FVC and FEV1/FVC range: • 18 - 39 years of age: ≥80% of predicted normal • 40 - 59 years of age: ≥75% of predicted normal • 60 - <80 years of age: ≥70% of predicted normal Pulmonary Function Test associated footnote "j" in Section 3.0 : "To be conducted within 7 days prior to dosing." was replaced by "j Pulmonary function test may be performed in the event of a pulmonary AE, if deemed clinically necessary by the Investigator or designee." PFT [spirometry] as part of safety monitoring: Spirometry measures will be taken at screening (within 7 days prior to dosing) using a standard calibrated spirometer to determine the parameters detailed below. Spirometry may be repeated during the study in response to pulmonary symptoms at the discretion of the Investigator or designee.

	• FEV1 (forced expiratory volume); • FVC (forced vital capacity); • FEV1/FVC. FEV_1 Forced expiratory volume FVC Forced vial capacity (Section 9.2.6)
In Section 1.0 – Study Summary, Section 6.1 - Study Design, and Section 9.2.6 – Pulmonary Function Test.	
Addition of the wording	Spirometry as the pulmonary function test may be performed in the event of a pulmonary AE, if deemed clinically necessary by the Investigator or designee.
In Section 3.0 – Schedule of Study Procedures – row for pulmonary function test	
Merging columns	The columns from screening until Day 10 were merged and indicated with a single X.
Change 2: The name of the study drug was changed to mobocertinib to match current IB	
Change of Wording	From TAK-788 to mobocertinib
Change 3. In Section 4.0 (Introduction), wording was updated to match the current IB and the study TAK-788-1008	
In Section 4.1 – Background, Section 4.3 – Benefit/Risk Profile, and Section 16.0 - References	
Wording Update	From IB Edition 3.0, Jan-2019 to IB Edition 4.0, 04-Jan-2020 and update of background information and benefit/risk information.
Change 4. In Section 9.2.9.1 - Clinical Laboratory Tests, renal function will be measured based on the MDRD; therefore, under "Chemistry", creatinine clearance is incorrectly listed as measured by Cockcroft-Gault formula. Additionally, protease will not be measured during the study, and typographical redundancy of listing amylase and lipase twice was corrected as only one sample will be taken.	
Wording removed	protease Duplicate analytes: amylase and lipase Footnote '*':".(…) creatinine clearance will be calculated using the Cockcroft-Gault formula."
Wording added	Footnote '*': (…) eGRF will be calculated based on MDRD for renal classification assignment."

Change 5. In Section 3.0 - Schedule of Study Procedures - a predose blood samples for protein binding of mobocertinib and metabolites will not be collected; therefore, the "X" should be removed from predose time points in "Blood for protein binding for mobocertinib and metabolites (AP32960 and AP32914).
Wording removed X
Change 6. In Section 9.2.4 - Vital Signs - The timing of the posture requirement is not listed in the protocol for vital sign measurements; therefore, the timing was added to the second paragraph.
Wording added (subjects must be seated for at least 5 minutes prior to measurement)
Change 7. In Section 9.2.5 - 12- Lead ECG - the timing of the posture requirement is not listed in the protocol for ECG measurements; therefore, the sentence was added to the second paragraph.
Wording added Subjects are required to be supine for at least 5 minutes prior to the ECG measurement.
Change 8. In Section 3.0 - Schedule of Study Procedures - the "Assessment of Renal Function" row has an incorrect footnote "g" that should be replaced by footnote "h" that lists the details of renal function assessment
Change 9. In Section 9.2.9.1 - Clinical Laboratory Tests (under 'Other') - subjects who test positive for HCV antibody will not be tested for RNA levels. This is in accordance with exclusion criterion 11 for healthy subjects and exclusion criterion 14 for subjects with RI (Sections 1.0 Study Summary and Section 7.2 Exclusion Criteria).
Wording removed (if antibody positive, confirm RNA negative)
Change 10. During the study, only two active metabolites of mobocertinib, AP32960 and AP32914, will be analyzed. Therefore, all references to possible analysis of other mobocertinib metabolites in Section 1 – Study Summary (under Study Design, Statistical Considerations, and Sample Size Justification), Section 3 - Schedule of Study Procedures, Section 4.2 - Rationale for the Proposed Study, Section 6.1 - Study Design, Section 6.3.5 – Critical Procedures Based on Study Objectives: Timing of Procedures, Section 9.3.1.1 Plasma PK Measurements, Section 9.3.1.2. – Urine PK Measurements, Section 11.1.3 Pharmacokinetic Analysis, were removed.
Wording removed including but not limited to
Change 11. COVID-19 tests were added at screening and check-in to mitigate infection risk.
In Section 3.0 – Schedule of Study Procedures, addition of a row indicating COVID-19 testing.
Wording added Row title COVID-19 test with 'X' marked at screening and check-in columns.
Addition of Exclusion criteria 12 in Section 1.0 – Study Summary and Section 7.2.1 – Exclusion Criteria for Healthy Subjects and exclusion criterion 15 in Section 1.0 – Study Summary and

Section 7.2.2 – Exclusion Criteria for Subjects with Renal Impairment.	
Wording added	Positive test result for COVID-19 testing at screening or check-in.
In Section 9.2.9.1 - Clinical Laboratory Tests (under 'Other'), addition of COVID-19 test	
Wording added	COVID-19 testing (performed according to CRU standard procedures detailed in a separate document[s])
Change 12: Subjects confinement in the CRU was extended to Day 10 to reduce the risk of subjects' being exposed to COVID-19.	
Confinement period, release time, and indication for return visits on Days 8 and 10 in Section 1 – Study Summary (under Study Design), Section 2.0 – Study Schematics, Section 3 – Schedule of Study Procedures, Section 6.1 – Study Design, and Section 10.2.6.2 – Reporting AEs, were updated.	
Wording removed	Study Design: Subjects will be furloughed from the CRU in the morning of Day 6 after the 120-hour PK sample collection and return to the CRU for additional PK sample collections in the morning of Days 8 and 10. The study will consist of a 21-day screening period, a 6-day confinement period (Day −1 to Day 6) and a follow-up phone call 30 ± 2 days after dosing. Study Schematics: Day 2-6 cell and indication for outpatient visits on Days 8 and 10 removed. Subjects will be confined on Day -1 and be released from confinement after the 120-hour study assessments (Day 6) are completed and will and will return to the study site for subsequent procedures on Days 8 and 10, as per the scheduled of study procedures (Section 9.0). Schedule of study procedures (footnote 'n'): Subjects will start the confinement on Day -1 and be released from confinement after the 120-hour study assessments (Day 6). Subjects may be required to remain at the CRU for longer at the discretion of the Investigator or designee. Reporting AEs: At each study visit, the Investigator will assess whether any subjective AEs have occurred.
Wording added	Study Design: Subjects will be confined in the CRU from Day -1 and be released from confinement after the 216-hour study assessments (Day 10) are complete. The study will consist 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.

	Study Schematics: Cell title for Days 8 and 10 changed to Days 2-10. Subjects will start the confinement on Day -1 and be released from confinement after the 216-hour study assessments (Day 10) are complete, as per the scheduled of study procedures (Section 9.0). Schedule of study procedures (footnote 'n'): Subjects will start the confinement on Day -1 and be released from confinement after the 216-hour study assessments (Day 10). Subjects may be required to remain at the CRU for longer at the discretion of the Investigator or designee. Reporting AEs: At follow-up, the Investigator will assess whether any subjective AEs have occurred.
Merging cells	The columns from Day-1 check-in until Day 10 were merged with an X. An X will retained at screening.

Typographical and grammatical corrections, as well as formatting changes, were made throughout the protocol.

Appendix F Detailed Description of Amendments to Text: Amendment 2

Change 1. Severe renal group classification based on eGFR values was changed from <30 mL/min/1.73 m^2 to 15-29 mL/min and normal renal function classification based on eGFR was changed from ≥ 90 mL/min/1.73 m^2 to ≥ 90 mL/min due to changes in recommendations in the new draft FDA guidance released September 2020 Pharmacokinetics in Patients With Impaired Renal Function —Study Design, Data Analysis and Impact on Dosing. For assessment of renal function, eGFR value will be calculated based on MDRD formula divided by standard BSA value of 1.73 m^2 for the renal classification category of subjects (ie, severe RI or normal renal function). For subjects with non-standard BSA, the eGFR value calculated by MDRD formula will be multiplied by the individual's BSA calculated using appropriate formula (Dubois and Dubois, 1916) and divided by 1.73 m^2.

The following sections were updated to reflect this change:

- Section 1.0 – Study Design, Study Subject Population, Criteria for Inclusion (Healthy Subjects [criterion #5], Subjects with Renal Impairment [criterion #5])
- Section 3.0-Schedule of Study Procedures (footnote h)
- Section 6.1 - Study Design
- Section 6.3.1 – Rationale of Study Design
- Section 7.1.1 – Inclusion Criteria for Healthy Subjects (criterion #5)
- Section 7.1.2 – Inclusion Criteria for Subjects with Renal Impairment (criterion #5)

Change 2. The planned sample size in each renal function arm was increased from 8 subjects to 12 subjects to provide a precise estimation of combined molar AUC_∞ of mobocertinib and its active metabolites AP32960, and AP32914 in subjects with severe renal impairment compared to healthy subjects with normal renal function. Details for the sample size estimation were also added to the appropriate sections.

The following sections were updated to reflect this change:

- Section 1.0 – Study Design, Planned Number of Subjects, and Sample Size Justification
- Section 6.1 - Study Design (Table 6.a)
- Section 7.8 – Subject Replacement
- Section 11.3 – Determination of Sample Size

Change 3. Body surface area (BSA) will be calculated based on Dubois and Dubois formula and a reference "Dubois D, EF Dubois, 1916, A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, Arch Intern Med, 17:863-871" was added to the protocol.

The following sections were updated to reflect this change:

- Section 1.0 – Study Design, Criteria for Inclusion (Healthy Subjects [criterion #5], Subjects with Renal Impairment [criterion #5])
- Section 3.0-Schedule of Study Procedures (footnote h)
- Section 6.1 - Study Design
- Section 16.0 - References

Change 4. The upper age limit of subjects was changed from 80 to 81 years old.

The following sections were updated to reflect this change:

- Section 1.0 – Criteria for Inclusion (Healthy Subjects [criterion #1], Subjects with Renal Impairment [criterion #1])
- Section 7.1.1 – Inclusion Criteria for Healthy Subjects (criterion #1)
- Section 7.1.2 – Inclusion Criteria for Subjects with Renal Impairment (criterion #1)

Change 5. The FDA guidance released September 2020 Pharmacokinetics in Patients With Impaired Renal Function —Study Design, Data Analysis and Impact on Dosing was updated to replace FDA guidance released March 2010.

The following sections were updated to reflect this change:

- Section 1.0 – Rationale for the Proposed Study
- Section 6.3.1 - Rationale of Study Design
- Section 6.3.3.1 – Pharmacokinetic Endpoints
- Section 16.0 - References

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	14-Dec-2020 13:39 UTC
[redacted]	Biostatistics Approval	14-Dec-2020 14:09 UTC
[redacted]	Clinical Science Approval	14-Dec-2020 14:14 UTC