Clinical Study Protocol	
Drug Substance	Savolitinib (AZD6094)
Study Code	D5082C00003
Version	6.0
Date	19 December 2018

A Phase III, Open Label, Randomised, Controlled, Multi-Centre Study to Assess the Efficacy and Safety of Savolitinib versus Sunitinib in Patients with MET-Driven, Unresectable and Locally Advanced, or Metastatic Papillary Renal Cell Carcinoma (PRCC)

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden*

VERSION HISTORY

Version 6.0, 19 December 2018

Overall changes

A recent review of the final results of the Molecular Epidemiology Study concluded that in this data-set, [redacted] It was also concluded that the SAVOIR study design would not benefit from a study size reassessment given the [redacted]

Following a review of the Molecular Epidemiology Study results, a decision, endorsed by the IDMC, was made to terminate recruitment into SAVOIR.

Patients randomised in SAVOIR may continue to receive their assigned treatment for as long as they are deriving clinical benefit or until they meet a protocol-defined stopping criterion and must follow the study plan as outlined. Patients already in screening (who have signed the ICF) will have the option to continue screening and to randomisation if eligible.

Consequential changes for clarity have been made in multiple sections throughout the protocol.

Changes in specific sections:

Whole document: Minor formatting changes have been made throughout (eg, table formatting to align with AZ style guide).

Section 1.4 (Study design): Rationale added as to why recruitment into SAVOIR has been terminated.

Figure 1 (Study flowchart) updated to remove 'n' numbers from the savolitinib and sunitinib dosing schedule. Abbreviations footnote also added for clarity.

Section 1.5.1 (Independent Data Monitoring Committee): Rationale added as to why recruitment into SAVOIR has been terminated, and why an interim analysis and sample size-reassessment will no longer take place.

Section 4.3.4 (Post study-drug follow up): Information regarding the management of patients' post-final analysis has been added.

Section 4.3.5 (Patient management post-final analysis): Section/information regarding the management of patients' post-final analysis has been added.

Section 8.1 (Statistical considerations):

Section revised to state that due to termination of recruitment into SAVOIR, all secondary analyses will be descriptive. Figure 2 (Multiple testing strategy) removed, as no longer relevant.

Text added regarding the updated sample size. The sample size has been reduced from approximately 180 patients to approximately 50 patients.

Rationale added as to why an interim futility analysis and sample size-reassessment will no longer take place.

Section 8.3.1.3 (Objective Response Rate (ORR): Text revised to state that only summaries for ORR will be provided.

Section 8.3.1.4 (Duration of Response (DoR): Text revised to state that only summaries for DoR will be provided.

Section 8.3.1.5 (Disease control rate (DCR): Text revised to state that only summaries for DCR will be provided.

Section 8.3.1.6 (Tumour shrinkage: Text revised to state that only summaries for tumour shrinkage will be provided.

Section 8.3.1.9 (HRQoL and symptoms): Text revised for how the FACIT-F and FKSI-19 questionnaire scores are calculated.

Section 8.4 (Methods for statistical analyses): Table 13 (Formal statistical analyses to be conducted and pre-planned sensitivity analyses) removed, as no longer relevant.

Section 8.4.1 (Analysis of the primary variable[s]): Section revised to clarify the analysis of the primary variable.

Section 8.4.2 (Analysis of the secondary variable[s]): Section revised to clarify the analysis of ORR and DCR, DoR, OS, PFS2, and PRO analyses.

Text revised to clarify the time period for OS and PFS2 analysis.

Section 8.4.3 (Subgroup analyses): Section updated to state that no subgroup analysis will be performed.

Section 8.4.4 (Interim analysis): Rationale added as to why an interim futility analysis will no longer take place. Information regarding the original interim futility analysis has been removed.

Section 8.4.5 (Sensitivity analysis): Text regarding evaluation-time bias and attrition bias has been removed, as no longer relevant.

Section 8.4.6.1 (Pharmacokinetics): Section revised for PK analysis.

Section 9.3 (Study timetable and end of study): Information removed regarding the original data cut off. Text regarding the stopping criteria for the final analysis has been added.

Appendix E (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law): Appendix revised in-line with an updated FDA requirement for reporting all PHL cases as SAEs.

Version 5.0, 03 August 2018

Overall changes

Safety information and management guidelines for QTc prolongation have been updated to align with the Project Specific Safety Requirements, which have been updated in response to health authority interactions based on findings from a positive thorough QT study. Exclusion criteria have been updated to clarify QTcF criteria. The schedule of ECG assessments has been updated and additional dose modification guidance for savolitinib-related QTcF prolongation has been added.

Changes in specific sections:

Section 3.2 (Exclusion criterion #17): Mean resting QT interval clarified (QTcF) and separate QTcF criteria added for men and women.

Section 4 (Study plan and timing of procedures), Table 1: Table text and footnotes updated to require triplicate ECG assessments throughout the study.

Section 5.2.3.1 (Resting 12-lead ECG): Schedule of ECG assessments updated to require triplicate ECG assessments throughout the study.

Section 6.8.1.4 (Dose modifications for savolitinib-related QTcF prolongation), Table 10: updated to include a consult with a cardiologist for Grade 3 and 4 toxicities and to clarify QTc interval (QTcF).

Version 4.0, 26 July 2018

Overall changes

Safety information and management guidelines for QTc prolongation have been updated to align with the Project Specific Safety Requirements which have been updated in response to findings from a positive thorough QT study. Exclusion criteria have been updated to clarify factors that may increase risk of QTc prolongation. Concomitant medication guidance on drugs known to prolong QT interval has been updated. The schedule of ECG assessments has been updated.

Changes in specific sections:

Whole document. For consistency, v4.03 has been removed from CTCAE throughout the whole document.

Section 1.3: Addition to benefit/risk text around QTc prolongation in response to findings from a thorough QT study.

Section 3.2 (Exclusion criterion #17): Factors that may increase risk of QTc prolongation clarified in response to findings from a thorough QT study

Section 3.6.2: Guidance on drugs that prolong QT interval added.

Section 5.2.3.1: Schedule of ECG assessments updated in response to findings from a thorough QT study.

Section 6.8.1: Addition of QTc prolongation to management of savolitinib-related toxicities in response to findings from a thorough QT study.

Section 6.8.1.4: Addition of QTc prolongation dose modification guidance in response to findings from a thorough QT study.

Section 6.8.1.5: Addition of QTc prolongation risk minimisation in response to findings from a thorough QT study.

Table 1: Schedule of ECG assessments updated in response to findings from a thorough QT study.

Appendix I: Addition of Appendix providing guidance on potential interactions of savolitinib with concomitant medications known to prolong QT interval.

Version 3.0, 09 May 2018

Changes to the protocol are summarised below.

Overall changes

Inclusion and exclusion criteria have been clarified. Text has been inserted to add clarity on the HBsAg, HBV DNA and HCV RNA testing. Information on the VEGF TKIs that are currently most used in PRCC treatment has been updated. Safety sections have been amended to align with updated product safety information and guidance. Other minor edits have been made included to improve consistency.

Changes in specific sections:

Whole document. For consistency, CTCAE has been updated to v4.03 throughout the whole document.

Section 1.3 (Benefit/risk and ethical assessment): Addition to benefit/risk of text around drug-induced liver injury, hypersensitivity and pyrexia to align with updated product safety information and guidance.

Sections 2.4 and 5.7.4 (exploratory endpoint): [redacted]

Section 3.1 (Inclusion criterion #3): Clarity has been added by inserting 'Patients with papillary urothelial carcinoma or renal pelvis cancer of the kidney are not considered PRCC and are not eligible'.

Section 3.1 (Inclusion criterion #4): Disease setting (advance setting) has been clarified.

Section 3.2 (Exclusion criterion #3): The wording has been revised to allow 28 days washout period for all agents.

Section 3.2 (Exclusion criterion #12): The type of HCV RNA test has been clarified.

Section 3.5 (Methods for assigning treatment groups): The VEGF TKIs that are currently most used in PRCC treatment has been updated.

Section 4 (Study plan and timing of procedures), Table 1: For Echocardiogram/MUGA procedure, an X has been added for the EOT visit as this was missing. In addition, pregnancy tests have been added on Day 1 of each cycle.

Section 4.1 (Screening/enrolment period): Clarification that patients may be enrolled based on pre-existing MET-driven result if available.

Section 5.2.1 (Laboratory safety assessments), Table 2: Leukocyte count has been added to 'U-Dipstick- Leukocyte esterase' as some sites do not perform Leukocyte esterase but perform a Leukocyte count instead.

Section 5.2.1 (Laboratory safety assessments), Table 2: Footnotes have been inserted/revised to clarify information about the HBsAg, HBV DNA and HCV RNA tests.

Section 5.2.5.1 (Serum or urine pregnancy test): Updated in light of a request from a Health Authority (Poland).

Section 6.3.3 (Variables): CTCAE grade revised to worst

Sections 6.8.1.1, 6.8.1.2 and 6.8.1.3: Re-ordered for clarity

Section 6.8.1.1 (Guidance for management of non-hepatic savolitinib specific toxicities): Hypersensitivity and pyrexia sections updated to align with updated product safety information and guidance.

Section 6.8.1.3 (Dose modifications for savolitinib-related toxicities), Table 9: Updated to align with updated product safety information and guidance.

Version 2.0, 12 May 2017

Changes to the protocol are summarised below.

Overall changes

Information regarding hypersensitivity and pyrexia has been added, to reflect the updated information in the Project Specific Safety Requirements (PSSR). The description of PFS2 has also been updated to clarify the intended assessments and analyses. Other minor edits are included to clarify specific passages of text in the protocol.

Changes in specific sections

Section 3.1 (Inclusion Criteria). Information regarding barrier contraception has been updated to reflect updated information in the PSSR.

Section 4.3.3 (Follow-up for second progression on subsequent anticancer therapy after PD by RECIST 1.1 [PFS2]). The description of PFS2 has been updated to clarify the intended assessments and analyses.

Section 6.8.1.3 (Guidance for management of non-hepatic savolitinib specific toxicities) has been created, and information regarding hypersensitivity and pyrexia has been added. Section 6.8.1.4 (Risk minimisation activities for identified and potential risks associated with savolitinib) has been updated to include pyrexia and hypersensitivity. 'Dermatologic' information has been moved to Section 6.8.1.3.

Version 1.0, 20 January 2017
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Phase III, Open Label, Randomised, Controlled, Multi-Centre Study to Assess the Efficacy and Safety of Savolitinib versus Sunitinib in Patients with MET-Driven, Unresectable and Locally Advanced, or Metastatic Papillary Renal Cell Carcinoma (PRCC)

International Co-ordinating Investigator

Toni K. Choueiri

Dana Farber Cancer Institute

440 Brookline Ave., Boston, MA 02215

[redacted]

Study site(s) and number of patients planned

Approximately 180 patients were planned to be randomised from 5 to 10 countries worldwide in approximately 50 to 75 sites. Recruitment to the study was closed on 22 November 2018. It is now estimated that approximately 50 patients will be randomised from 7 countries.

Study design

This is an open label, randomised, multicentre, global Phase III study designed to evaluate the efficacy of savolitinib compared with sunitinib in patients with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma (PRCC). Patients can be treatment naïve or previously treated but cannot have previously received sunitinib or a MET inhibitor.

Following signature of the Part 1 Informed Consent Form (ICF), the MET-driven status of the tumour will be determined in archival or, if necessary, fresh tumour by targeted Next Generation Sequencing (NGS) in the sponsor-designated central laboratory. Patients with confirmed MET-driven tumours, based on this testing or based on a pre-existing MET-driven result from the Sponsor-designated laboratory, may then sign the main study (Part 2) ICF. The Part 2 screening assessments must take place within 28 days of signing the ICF for Part 2. Randomisation must take place within 28 days of signing the ICF for Part 2. Patients who fulfil all the eligibility criteria will be randomised in a ratio of 1:1 to receive savolitinib

(600 mg for patients ≥50 kg and 400 mg for patients <50 kg PO QD) or sunitinib (50 mg PO QD). Patients will be stratified based on International Metastatic RCC Database Consortium (IMDC) risk category as well as whether they are treatment naive vs. previously treated with or without a VEGF-TKI. For the purposes of planning, a 6-week period will be called a "cycle". Treatment with sunitinib will be given daily for 4 weeks on/2 weeks off. Treatment with savolitinib will be given continuously. There is no maximum duration of treatment and patients will continue to receive study medication until one of the discontinuation criteria are met.

Following randomisation, patients will attend scheduled study visits as outlined in the study plan. Efficacy will be assessed by objective tumour assessments at baseline and every 6 weeks (±7 days) during the first year (at the start of each cycle) and then every 12 weeks thereafter until disease progression as defined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and confirmed by Blinded Independent Central Review (BICR). Patients will receive study treatment until one of the treatment discontinuation criteria is met; there is no maximum duration of treatment.

Regardless of initial treatment, patients will have two options for post-progression therapy following BICR-confirmation of progressive disease (PD):

1 Receive subsequent non-study anti-cancer therapy that does not contravene local practice.
2 Continue to receive the assigned treatment as long as in the opinion of the investigator, the patient is deriving benefit and the patient meets the original eligibility criteria in terms of Performance Status and laboratory values. This decision must be discussed with and approved by the AstraZeneca study physician. Such patients will continue to undergo monitoring as per the Study Plan (Table 1).

There will be no cross-over.

Following discontinuation of study medication for PD by RECIST 1.1 as determined by Investigator assessment, patients that started on subsequent cancer therapy post-progression will continue to be followed at least every 12 weeks by investigator assessment for documentation of second progression. Determination of PD for second progression-free survival (PFS2) will be by institutional call. Patients who choose to continue on study therapy after PD as determined by investigator assessment will not be considered to have a second progression-free survival (PFS) event until they discontinue study medication and progress on subsequent anti-cancer treatment.

In the Overall Survival (OS) follow-up period following PFS2, all subsequent therapies and vital status will be documented at least every 12 weeks until death, lost to follow-up, withdrawal of consent, or end of study, whichever comes first.

A recent review of the final results of the Molecular Epidemiology Study (MES) concluded that in this data-set, [redacted] It was also concluded that the SAVOIR study design would not benefit from a study size reassessment [redacted]

Following a review of the MES results, a decision, endorsed by the Independent Data Monitoring Committee (IDMC), was made to terminate recruitment into SAVOIR.

Patients randomised in SAVOIR may continue to receive their assigned treatment for as long as they are deriving clinical benefit or until they meet a protocol-defined stopping criterion and must follow the study plan as outlined. Patients already in screening (who have signed the ICF) will have the option to continue screening and to be randomised if eligible.

Further information can be found in the statistical methods section below.

Objectives

Primary Objective:	**Outcome Measure:**
To determine the efficacy of savolitinib when compared to sunitinib in patients with MET-driven, unresectable and locally advanced, or metastatic PRCC	• PFS (time to earliest progression as defined by RECIST 1.1 and confirmed by BICR, or death)

Secondary Objective:	**Outcome Measure:**
To compare the efficacy of savolitinib versus sunitinib in patients with MET-driven, unresectable and locally advanced, or metastatic PRCC	• Overall Survival (OS) • Objective Response Rate (ORR), duration of response (DoR) and best percentage change in tumour size by BICR using RECIST 1.1 criteria • Disease Control Rate (DCR) at 6 and 12 months
To assess the impact of savolitinib and sunitinib on disease related symptoms and health-related QOL in this patient population	• Mean change from baseline in FKSI-19 and FACIT-F scores
To evaluate the pharmacokinetics of savolitinib in this patient population	• PK concentration data
Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of savolitinib in relation to sunitinib	• Adverse events [AEs] and serious adverse events [SAE] as characterised and graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Event [CTCAE], collection of clinical chemistry/haematology parameters, liver function tests, echocardiograms and electrocardiograms (ECGs), vital signs including blood pressure (BP) and heart rate

Exploratory Objective:	**Outcome Measure:**
To compare the efficacy of savolitinib versus sunitinib in patients with MET-driven, unresectable and locally advanced, or metastatic papillary renal cell carcinoma PRCC	• Time from randomisation to objective disease progression on subsequent anti-cancer therapy following PD by RECIST 1.1 on study medication, or death (PFS2)
To assess the impact of savolitinib vs. sunitinib on patient reported AEs	• Collection of PRO CTCAE symptoms
To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason for hospitalisations and unscheduled clinic visits, procedures undertaken and length of hospital inpatient stays • Health state response and utility index derived from the EQ-5D-5L
[redacted]	[redacted]
To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional)	• Pharmacogenetic analyses on blood samples
[redacted]	[redacted]

The exploratory analyses may not be reported in the clinical study report (CSR). They may be reported separately and may also form part of a pooled analysis with other studies.

Target patient population

The target population for this study includes previously treated or untreated patients with MET-driven, unresectable and locally advanced, or metastatic PRCC without co-occurring *FH* or *VHL* mutations. Patients cannot have previously received sunitinib or a MET-inhibitor. Confirmation of MET-driven PRCC without co-occurring *FH* or *VHL* mutations by a validated NGS assay in the sponsor-designated central laboratory is required prior to study entry.

Duration of treatment

Patients will receive either savolitinib or sunitinib until one of the treatment discontinuation criteria is met. There is no maximum duration of treatment.

Investigational product, dosage and mode of administration

Savolitinib will be administered continuously as three 200 mg tablets by mouth (PO) with a meal once daily (QD) (for patients ≥50 kg) or two 200 mg tablets PO with a meal QD (for patients <50 kg). The comparator will be sunitinib, given as two 25 mg capsules PO daily, with or without food for 4 weeks on/ 2 weeks off.

Statistical methods

The initial assumption was that the true treatment effect had a hazard ratio (HR) of 0.6 (which would have translated to an approximate 3-month improvement in median PFS over an assumed 4-month median PFS for MET-driven patients on sunitinib, assuming PFS was exponentially distributed), 121 PFS events confirmed by BICR would have had to have been observed for the study to have 80% power to show a statistically significant difference in PFS at the two-sided 5% level. The smallest treatment difference that would have been statistically significant at the final analysis was a PFS HR of 0.69. Assuming 67% maturity, 180 patients would have been needed to be randomised. An interim futility analysis of PFS was planned to be conducted when a total of approximately 36 BICR-confirmed PFS events had been observed (30% of 121 PFS events, which was estimated to occur 17 months after the first patient had been randomised). Following IDMC endorsement to terminate recruitment into SAVOIR, the interim analysis will not occur. However, interim reviews of safety data by the IDMC will continue until end of study.

The final analysis of all endpoints will be conducted at the earliest time when the following 2 criteria are met:

1 36 PFS events by investigator assessment
2 The opportunity to have at least 7.5 months follow-up from randomisation

If criterion #1 has not been met 12 months after last subject in, the final analysis will be performed.

The primary statistical analysis for efficacy will be carried out in the intent-to-treat population. Treatment effect will be compared between treatment groups on the basis of randomised treatment, regardless of the treatment actually received. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of randomised treatment (savolitinib or sunitinib). The safety data will be summarised descriptively and difference between treatment arms will not be tested for statistical significance.

Primary endpoint (PFS) analysis will be conducted using a log rank test stratified by baseline stratification factors, providing that there are enough events in each stratum. The stratified HR together with its 95% confidence interval (CI) and p-value will be presented (an HR <1

will favour savolitinib). The primary endpoint PFS data will be based on tumour assessments by a blinded independent central review (BICR) of disease progression by RECIST 1.1. In addition, a sensitivity analysis will be performed using the investigator-recorded assessments.

Due to termination of recruitment into SAVOIR, all secondary endpoints will be descriptive. No subgroup analysis will be performed.

Objective tumour response rates and duration of response based on BICR using RECIST 1.1 will be presented for the two treatment arms.

Time from randomisation to investigator-assessed second progression on subsequent non-study anti-cancer therapy following PD using RECIST 1.1 while on study medication, or death (PFS2) will be summarised, and Kaplan Meier plots will be provided.

Appropriate summaries of exploratory outcome variables will be produced and compared across the two treatment arms.

[redacted]

[redacted]

Following IDMC endorsement to terminate recruitment into SAVOIR, a sample size-reassessment will no longer be performed.

TABLE OF CONTENTS PAGE

TITLE PAGE 1
VERSION HISTORY 2
CLINICAL STUDY PROTOCOL SYNOPSIS 10
TABLE OF CONTENTS 16
LIST OF TABLES 20
LIST OF FIGURES 21
LIST OF APPENDICES 21
1. INTRODUCTION 27
1.1 Background and rationale for conducting this study 27
1.1.1 Renal cell carcinoma 27
1.1.2 PRCC and MET pathway 28
1.1.3 Savolitinib/AZD6094 (HMPL-504) 29
1.1.3.1 Pharmacokinetics 29
1.1.3.2 Pharmacology and safety 29
1.1.3.3 Clinical antitumour activity data in patients with PRCC 29
1.1.3.4 Clinical monotherapy safety data 30
1.2 Rationale for study design, doses and control groups 31
1.2.1 Research hypothesis 31
1.2.2 Rationale for Savolitinib in PRCC 31
1.2.3 Rationale for sunitinib as comparator 31
1.2.4 Rationale for line-agnostic study 32
1.2.5 Rationale for exclusion of patients with co-occurring *FH/VHL* mutations 32
1.3 Benefit/risk and ethical assessment 33
1.4 Study design 34
1.5 Study governance and oversight 39
1.5.1 Independent Data Monitoring Committee 39
2. STUDY OBJECTIVES 40
2.1 Primary objective 40
2.2 Secondary objectives 40
2.3 Safety objectives 40
2.4 Exploratory objectives 40
3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL 41
3.1 Inclusion criteria 41
3.2 Exclusion criteria 43
3.3 Patient enrolment and randomisation 45

3.4 Procedures for handling incorrectly enrolled or randomised patients 46
3.5 Methods for assigning treatment groups 46
3.6 Restrictions 47
3.6.1 Need for contraception 47
3.6.2 Prohibited concomitant medications and treatments 48
3.7 Post-progression therapy 49
3.8 Discontinuation of investigational product 49
3.8.1 Procedures for discontinuation of a patient from study treatment prior to BICR-confirmed PD 50
3.9 Criteria for withdrawal from the study 51
3.9.1 Screen failures 51
3.9.2 Withdrawal of the informed consent 51
3.10 Discontinuation of the study 52
4. STUDY PLAN AND TIMING OF PROCEDURES 52
4.1 Screening/enrolment period 60
4.2 Treatment period 60
4.3 Post study-drug follow up 60
4.3.1 End of Treatment (EOT) 60
4.3.2 Safety follow-up 61
4.3.3 Follow-up for second progression on subsequent anti-cancer therapy after PD by RECIST 1.1 (PFS2) 61
4.3.4 Overall survival follow-up 62
4.3.5 Patient management post-final analysis 62
5. STUDY ASSESSMENTS 63
5.1 Efficacy assessments 63
5.1.1 Tumour assessments by CT or MRI scans (RECIST 1.1) 63
5.1.2 Tumour evaluation 64
5.1.3 Central reading of scans/BICR 64
5.2 Safety assessments 65
5.2.1 Laboratory safety assessments 65
5.2.2 Physical examination 67
5.2.3 ECG, ECHO/MUGA 67
5.2.3.1 Resting 12-lead ECG 67
5.2.3.2 ECHO or MUGA 67
5.2.4 Vital signs 68
5.2.4.1 Pulse and blood pressure 68
5.2.4.2 Body temperature 68
5.2.5 Other safety assessments 68
5.2.5.1 Serum or urine pregnancy test 68
5.3 Other assessments 68
5.3.1 Patient Reported Outcomes 68
5.3.1.1 Functional Assessment of Chronic Illness Therapy – Fatigue 70
5.3.1.2 Functional Assessment of Cancer Therapy Kidney Symptom Index-19 70

5.3.1.3 European Quality of Life-5 Dimensions-5 Levels 70
5.3.1.4 PRO CTCAE 70
5.3.2 Hospital resource use 71
5.4 Pharmacokinetics 71
5.4.1 Collection of samples 71
5.4.2 Determination of drug concentration 72
5.4.3 Storage and destruction of pharmacokinetic samples 72
5.5 Pharmacodynamics 73
5.5.1 Collection of samples 73
5.6 Pharmacogenetics (Appendix C) 73
5.7 Biomarker analysis 73
5.7.1 NGS analysis to determine MET-driven status of tumour biopsy sample 73
5.7.2 Collection, analysis and reporting of tumour samples 74
5.7.3 Exploratory use of data generated from the sponsor-designated central laboratory testing of tumour samples 74
[redacted]
5.7.7 Collection of tumour samples for exploratory analysis at disease progression (optional) 77
5.7.8 Storage, re-use and destruction of biological samples 77
5.7.9 Labelling and shipment of biological samples (Appendix B) 77
5.7.10 Chain of custody of biological samples 77
5.7.11 Withdrawal of Informed Consent for donated biological samples 78
5.7.12 Volume of blood 78
6. SAFETY REPORTING AND MEDICAL MANAGEMENT 79
6.1 Definition of adverse events 79
6.1.1 AEs of special interest – hepatic disorders 80
6.2 Definitions of serious adverse event 81
6.3 Recording of adverse events 81
6.3.1 Time period for collection of adverse events 81
6.3.2 Follow-up of unresolved adverse events 81
6.3.3 Variables 82
6.3.4 Causality collection 83
6.3.5 Adverse events based on signs and symptoms 83
6.3.6 Adverse events based on examinations and tests 83
6.3.7 Hy's Law 84
6.3.8 Disease progression 84
6.4 Reporting of serious adverse events 84
6.5 Overdose 85
6.6 Pregnancy 85
6.6.1 Maternal exposure 86
6.6.2 Paternal exposure 86

6.7 Medication error 86
6.8 Management of study medication-related toxicities - dose reductions and modifications 88
6.8.1 Management of savolitinib-related toxicities 88
6.8.1.1 Guidance for management of savolitinib specific toxicities 89
6.8.1.2 Dose modification due to savolitinib-related hepatotoxicity 89
6.8.1.3 Dose modifications due to other savolitinib-related toxicity 91
6.8.1.4 Dose modifications for savolitinib-related QTcF prolongation 92
6.8.1.5 Risk minimisation activities for identified and potential risks associated with savolitinib 92
6.8.2 Management of sunitinib-related toxicities 95
6.8.2.1 Risk minimisation activities for risks associated with sunitinib 95
7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS 97
7.1 Identity of study medications 97
7.2 Dose and treatment regimens 97
7.2.1 Savolitinib 97
7.2.2 Sunitinib 98
7.3 Labelling 99
7.4 Storage 99
7.5 Compliance 99
7.6 Accountability 99
7.7 Concomitant and other treatments 99
7.7.1 Permitted concomitant medications and treatments 99
7.7.2 Restrictions based on clinical pharmacology for both study medications 100
7.7.3 Other concomitant treatment 101
8. STATISTICAL ANALYSES BY ASTRAZENECA 101
8.1 Statistical considerations 101
8.2 Definitions of analysis sets 102
8.2.1 Full analysis set 102
8.2.2 Safety analysis set 102
8.2.3 PK analysis set 102
8.3 Outcome measures for analyses 103
8.3.1 Calculation or derivation of efficacy variables 103
8.3.1.1 Blinded Independent Central Review (BICR) of RECIST-based assessments 103
8.3.1.2 Progression-Free Survival (PFS) 103
8.3.1.3 Objective Response Rate (ORR) 104
8.3.1.4 Duration of Response (DoR) 104
8.3.1.5 Disease control rate (DCR) 104
8.3.1.6 Tumour shrinkage 104
8.3.1.7 Overall Survival (OS) 105
8.3.1.8 Time to second progression or death (PFS2) 105
8.3.1.9 HRQoL and symptoms 105
8.4 Methods for statistical analyses 106

8.4.1 Analysis of the primary variable (s) 106
8.4.2 Analysis of the secondary variable(s) 106
8.4.3 Subgroup analysis 108
8.4.4 Interim analysis 108
8.4.5 Sensitivity analysis 108
8.4.6 Exploratory analyses 108
8.4.6.1 Pharmacokinetics 108
8.4.6.2 Pharmacogenetic research and statistical methods, and determination of sample size 108
9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA 109
9.1 Training of study site staff 109
9.2 Monitoring of the study 109
9.2.1 Source data 109
9.2.2 Study agreements 110
9.2.3 Archiving of study documents 110
9.3 Study timetable and end of study 110
9.4 Data management by AstraZeneca 110
9.4.1 Serious Adverse Event (SAE) reconciliation 111
9.4.2 Data management of genotype data 111
9.4.3 Data associated with human biological samples 111
9.4.4 Management of external data 111
10. ETHICAL AND REGULATORY REQUIREMENTS 112
10.1 Ethical conduct of the study 112
10.2 Patient data protection 112
10.3 Ethics and regulatory review 112
10.4 Informed consent 113
10.5 Changes to the Clinical Study Protocol and Informed Consent Form 114
10.6 Audits and inspections 114
11. LIST OF REFERENCES 115

LIST OF TABLES

Table 1 Study schedule: Screening, On Study Treatment, Discontinuation and Follow-up 53
Table 2 Standard Laboratory Safety Assessment Panel 66
Table 3 Pharmacokinetic savolitinib blood sampling schedule 72
[redacted]

Table 7 Volume of blood to be drawn from each patient in the first 24 weeks 79
Table 8 Dose level reductions of study medications 88
Table 9 Dose modifications for savolitinib-related toxicities 91
Table 10 Dose modifications for savolitinib-related QTcF prolongation 92
Table 11 Dose modifications for sunitinib-related toxicities (including hepatic) 95
Table 12 IP strength and manufacturer 97

LIST OF FIGURES

Figure 1 Study flowchart 38

LIST OF APPENDICES

Appendix A Additional Safety Information 119
Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document 121
Appendix C Genetic Research 122
Appendix D Acceptable Birth Control Methods 125
Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law 126
Appendix F Guidance for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours) 131
Appendix G Performance Status (Karnofsky Scale) 139
Appendix H Guidance Regarding Potential Interactions of Savolitinib with Concomitant Medications 140
Appendix I Guidance Regarding Potential Interactions of Savolitinib with Concomitant Medications Known to Prolong QT Interval 145
Appendix J Patient Reported Outcomes 146
Appendix K Stages of Heart Failure – New York Heart Association Classification 157

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-HBc	Anti-hepatitis B core antigen
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AZRand	AstraZeneca Randomisation system
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BID	Twice a day
BP	Blood pressure
eCRF	Electronic Case Report Form
CA-125	cancer antigen 125
ccRCC	Clear cell Renal Cell Carcinoma
CHF	Congestive Heart Failure
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum serum concentration
CR	Complete Response
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Assay
CTCAE	Common Terminology Criteria for Adverse Event
[redacted]	[redacted]
DCR	Disease Control Rate
DES	Data Entry Site

Abbreviation or special term	Explanation
DGR	Dangerous Goods Regulations
DHEA	Dehydroepiandrosterone
DILI	Drug-induced liver injury
dL	Decilitre
DNA	Deoxyribonucleic acid
DoR	Duration of response
DUS	Disease under study
DVT	Deep vein thrombosis
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EE	Ethinyl Estradiol
EM	Erythema multiforme
ePRO	Electronic Patient Reported Outcomes
EOT	End of Treatment
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
EQ-VAS	EuroQoL-Visual Analogue Scale
EuroQoL	European Quality of Life
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full analysis set
FDG-PET	Fluorodeoxyglucose- Positron Emission Tomography
FFPE	Formalin Fixed and Paraffin Embedded
FH	Fumarate Hydratase
FKSI-19	Cancer Therapy Kidney Symptom Index-19
FSH	Follicle stimulating hormone
FTIH	First Time in Human
FU	Follow up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-macrophage colony stimulating factor

Abbreviation or special term	Explanation
GMP	Good Manufacturing Practice
HBsAg	Surface antigen of the hepatitis B virus (HBV)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
Hgb	Haemoglobin
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HL	Hy's Law
HOSPAD	Hospital Admissions module
HR	Hazard ratio
HRQoL	Health Related Quality of Life
i.v.	Intravenous
IATA	International Airline Transportation Association
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IC_{50}	Fifty percent of the maximal inhibitory concentration
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMDC	International Metastatic RCC Database Consortium
IMP	Investigational Medicinal Product
INR	International Normalisation Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intra-uterine device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LIMS	Laboratory Information Management System
LOEL	Lowest observed effect level
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MES	Molecular Epidemiology Study
mL	Millilitre
Mm	Millimetre
mmHg	Millimetre of mercury
MRI	Magnetic Resonance Imaging
mTOR	Mammalian target of rapamycin
MUGA	Multigated acquisition scan
NA	Not applicable
NADPH	Nicotinamide adenine dinucleotide phosphate-oxidase
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next Generation Sequencing
nM	Nanomolar
NOEL	No observed effect level
NTL	Non-target Lesion
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall survival
PAS	Primary Analysis Set
PD	Progression of Disease
PDA	Personal Data Assistant
PDL-1	Programmed cell Death Ligand-1
PFS	Progression-free survival
PFS2	Second progression-free survival
Pgp	P-glycoprotein
PGx	Pharmacogenetic
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetic
PO	Orally
PR	Partial Response
PRCC	Papillary renal cell carcinoma
PRO	Patient Reported Outcomes
PRO-CTCAE	The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

Abbreviation or special term	Explanation
PTT	Partial thromboplastin time
QD	Once a day
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's Correction Formula
RANK	Receptor activator of nuclear factor kappa
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RR	Response rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable Disease
SJS	Stevens-Johnson syndrome
SMQ	Standard MedDRA Query
SPC	Summary of Product Characteristics
SPF	Sun Protection Factor
$T_{1/2}$	Half-life
TBL	Total Bilirubin
TCGA	The Cancer Genome Atlas Research Network
TEN	Toxic epidermal necrolysis
TKIs	Tyrosine kinase inhibitors
TL	Target Lesion
tmax	Time to reach maximum concentration
ULN	Upper limit of normal
UV	Ultraviolet
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VEGF-TKI	Vascular endothelial growth factor receptor tyrosine kinase inhibitor
VHL	Von Hippel–Lindau
w/o	Without
WBDC	Web-based data capture
WHO	World Health Organization

Abbreviation or special term	Explanation
WoCBP	Women of Child Bearing Potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Renal cell carcinoma

Renal cell carcinoma (RCC) accounts for approximately 3% of all malignancies in adults (Bellmunt and Dutcher 2013). An estimated 62,700 Americans will be newly diagnosed with cancer of the kidney and renal pelvis and 14,240 Americans will die of this disease in the United States in 2016 (Siegel RL, Miller KD, Jemal A. 2016). Worldwide, 270,000 new patients are diagnosed each year and up to 116,000 deaths occur due to RCC (Ljungberg et al 2011). RCC is more common in men than in women and usually occurs between 50 to 70 years of age. Renal cell carcinoma is a heterogeneous disease made up of several histological subtypes with different genetic and biochemical characteristics. Among the histologic variants of RCC, clear cell RCC (ccRCC) is the most common, accounting for 75% to 90% of all renal malignancies. Papillary RCC (PRCC) is the most common of the non-clear cell renal carcinomas, accounting for 10% to 15% (Bellmunt and Dutcher 2013).

At present, there is no approved therapy indicated specifically for the treatment of PRCC, and therefore patients with PRCC are treated in a similar manner as clear-cell RCC patients. In addition, there has never been a rigorously controlled biomarker-based clinical trial to help inform the selection of treatment for patients with either ccRCC or PRCC (Bellmunt and Dutcher 2013). Chemotherapy trials have shown RCC to be resistant to cytotoxic treatments (Motzer et al 2002). Advances in ccRCC treatment have included anti-tumour agents that function as inhibitors of vascular endothelial growth factor (VEGF) angiogenesis and the mammalian target of rapamycin (mTOR). Approved agents targeting the VEGF pathway include, sunitinib, sorafenib, bevacizumab (in combination with IFN-α), pazopanib, and axitinib, and for targeting the mTOR pathway, temsirolimus, and everolimus. The combination of a VEGF-inhibitor and an mTOR inhibitor, lenvantinib and everolimus, was approved in 2016, as was cabozantinib, a small molecule with both VEGF- and MET-inhibitory properties. In 2015 nivolumab, an agent targeting the PD 1/programmed cell death ligand-1 (PDL-1) pathway, was approved. The trials that led to the approval of these agents almost exclusively included patients with ccRCC.

Studies exploring treatment efficacy in patients with both ccRCC and non-ccRCC, including PRCC suggest that current therapies allow patients with ccRCC to live longer than those with non-ccRCC (Kroeger et al 2013, Vera-Badillo et al 2015). A large retrospective analysis conducted in the International Metastatic RCC Database Consortium (IMDC) (Kroeger et al 2013) analysed 2370 patients who received first line targeted therapy between 2003 and 2012.

The prognosis for non-ccRCC was found to be worse than that of ccRCC. The median OS for PRCC patients was 14.0 months (95% CI 10.9, 17.1) and for ccRCC patients was 22.3 months (95% CI 20.7, 23.5). After adjustment for IMDC risk group, the HR for death was 1.57 (95% CI: 1.27 – 1.94; p<0.0001).

Taking into consideration the totality of the published evidence, the clinical practice guidelines of the European Society of Medical Oncology (Escudier et al 2014) and the National Comprehensive Cancer Network (NCCN; v. 2.2017, dated October 31, 2016) both recommend a clinical trial as the preferred option for treatment of advanced or metastatic PRCC patients. The 2014 guidelines for the European Association of Urology indicate that everolimus and sunitinib "remain options in this population, with a preference for sunitinib", but also indicate that patients should be referred for clinical trials where appropriate (Ljungberg et al 2015).

1.1.2 PRCC and MET pathway

With better understanding of tumour biology, there is now evidence that the MET pathway in patients with PRCC is often activated, which is thought to drive disease progression. There is a growing body of evidence suggesting that *MET* abnormalities are not only a differentiating characteristic of PRCC, but may be, in at least a subset of PRCC, a therapeutic target (The Cancer Genome Atlas Research Network 2016). Specifically, one of the underlying pathogenic features of PRCC is dysregulation of the MET signalling pathway, which is involved in cell motility, proliferation, angiogenesis, and cell survival. Overexpression of cytoplasmic MET has been reported in approximately 80% of papillary tumours in 2 series (Bellmunt and Dutcher 2013, Sweeney et al 2002) and in one study, correlated with higher stage tumours (Sweeney et al 2002).

MET is a transmembrane receptor tyrosine kinase essential for embryonic development and wound healing normally activated through interaction with its specific ligand, hepatocyte growth factor (HGF). During tumourigenesis, activation of the MET pathway triggers tumour growth, promotes tumour angiogenesis, and induces tumour metastases. Aberrant MET activation in tumour can be achieved by four different ways: (a) *MET* amplification, (b) MET protein overexpression, (c) *MET* activating mutations and (d) by the formation of an HGF/ MET autocrine/paracrine loop. Mutations in the tyrosine kinase domain of *MET* have been identified in patients with a hereditary form of PRCC, directly implicating MET in human tumourigenesis (Schmidt et al 1997, Jeffers et al 1997). In addition, trisomy of chromosome 7 (the location of both *MET* and *HGF*) is present in a high proportion of patients with PRCC, ranging from 40% to 75% of patients, and is thought to be a hallmark of this subtype of RCC (Choueiri et al 2013, Klatte et al 2009, Kovacs 1993, Fischer et al 1998). Evidence supporting the validity of MET as a therapeutic target in PRCC patients comes from the results of a Phase II study of foretinib (a multikinase inhibitor targeting MET, VEGF, and other receptors) in sporadic and hereditary PRCC (N=74) (Choueiri et al 2013). The ORR was 13.5% in the

overall population; however, the presence of germline *MET* mutations correlated strongly with foretinib activity (5 of 10 versus 5 of 57 patients with and without germline *MET* mutations, respectively). One of five patients with a somatic *MET* mutation had a Partial Response (PR).

1.1.3 Savolitinib/AZD6094 (HMPL-504)

Savolitinib (also known as AZD6094, HMPL-504 or volitinib) is a potent and selective ATP competitive, small molecule MET kinase inhibitor, with enzymatic and cellular IC_{50}s of 4 nM and <10 nM, respectively. It potently inhibits MET autophosphorylation and cell functions related to MET phosphorylation such as HGF-dependent or -independent tumour cell proliferation. Consistent with its potent enzyme and cell activity, savolitinib was found to inhibit cell growth in vitro in tumours with *MET* amplification in the absence of HGF-stimulation with IC_{50}s generally below 10 nM. It also potently inhibited HGF-stimulated cell proliferation in tumours with MET overexpression or carrying a HGF/MET autocrine loop. In human xenograft models in the mouse, savolitinib demonstrated antitumour activity against *MET*-amplified gastric and lung tumours with the median effective dose (ED_{50}) below 5 mg/kg following QD oral treatment.

1.1.3.1 Pharmacokinetics

The data collected following single dosing in the first-time-in-human (FTIH) study suggest that savolitinib is rapidly absorbed at all doses with the geometric mean (minimum-maximum) time to reach maximum concentration (t_{max}) ranging from 1 hour to 3 hours (0.5 to 6.2) across all regimens. Savolitinib was absorbed PO with high exposures. The $t_{1/2}$ ranged from 3.6 hours to 6.8 hours. Data from the food effect study in normal volunteers suggest that the major route of clearance for savolitinib is likely to be metabolism.

1.1.3.2 Pharmacology and safety

[redacted]

1.1.3.3 Clinical antitumour activity data in patients with PRCC

Preliminary evidence of clinical activity and biomarker data collected in the FTIH dose-escalation savolitinib study demonstrated that patients with PRCC and *MET* copy number gains via amplification or chromosome 7 gain may benefit from single-agent

treatment with savolitinib (Gan et al 2015). Of the 8 PRCC patients in the FTIH study treated at various doses and schedules, five harboured *MET* copy number gains by one of these mechanisms. Of these 5 patients, 3 patients (2 treated at 600 mg QD and 1 at 1000 mg QD) are partial responders, and a fourth received benefit as evidenced by a 25% decrease change in tumour measurements from baseline. Of the 3 partial responders, 1 patient with *MET* focal amplification remained in the study for 72 weeks, two patients with chromosome 7 gain remained on savolitinib for 39 and 147 weeks respectively. Of note, the PRCC patients that did not have *MET* alterations did not respond to treatment.

In the Phase II PRCC study (clinicaltrials.gov identifier: NCT02127710), archival tumour samples were mandated for exploratory biomarker analysis. As of November 2016, ninety of the 109 enrolled patients had sufficient tumour submitted for analysis of MET status and of these, 44 patients were found to have tumours that are MET-driven (ie, chromosome 7 gain, *MET* focal amplification, *MET* kinase domain mutations, *HGF* amplification, or any combination of these alterations) and 46 patients have MET-negative tumours. All patients have had 12 months of follow-up.

An ORR of 18.4% (8/44 patients) has been observed in the patients with MET-driven disease; no PR or CR were observed in the 46 MET-negative and 19 MET-unknown patients. The median PFS (and 95% confidence interval) was 24.7 weeks (17.7, 35.4), 6.4 weeks (6.1, 11.9) and 12.1 weeks (6.1, 33.6) in the MET-positive, MET-negative and MET-unknown patients, respectively (p=0.0003). Median PFS is 24.7 weeks in the patients with MET-driven tumours compared with 6.4 weeks in the patients with MET-negative tumours.

Based on this data set, a validated NGS assay which can detect chromosome 7 gain, *MET* amplification, *MET* kinase domain mutations, and *HGF* amplification will be used to prospectively determine eligibility for this trial.

1.1.3.4 Clinical monotherapy safety data

Savolitinib has been administered at various doses ranging from 100 mg to 1000 mg per day. As of January 2016, an estimated 233 patients had received at least 1 dose of savolitinib as monotherapy. To date, the majority of patients have received monotherapy savolitinib at 500 mg BID (60 patients) and 600 mg QD (125 patients).

Eighty-five percent (198/233) of patients had an AE that was considered by the investigator to be related to savolitinib treatment. The most frequently reported causally related AEs (≥5% of patients overall) were nausea (97/233 patients, 41.6%), vomiting (56/233 patients, 24.0%), fatigue (49/233 patients, 21.0%), peripheral oedema (34/233 patients, 14.6%), decreased appetite (29/233 patients, 12.4%), diarrhoea (23/233 patients, 9.9%), blood creatinine increased (20/233 patients, 8.6%), ALT increased (19/233 patients, 8.2%), AST increased (19/233 patients, 8.2%), and constipation (12/233 patients, 5.2%).

Causally related SAEs reported in more than 1 patient were: increased ALT and abnormal hepatic function (each reported in 4 patients); increased ALT and liver injury (each reported in 3 patients); and increased AST, drug-induced liver injury, and pyrexia (each reported in 2 patients). See section 6.1.1 for AEs of special interest for savolitinib.

1.2 Rationale for study design, doses and control groups

1.2.1 Research hypothesis

The research hypothesis is that savolitinib monotherapy will be more effective than sunitinib monotherapy in patients with MET-driven, unresectable and locally advanced, or metastatic papillary renal cell carcinoma (PRCC), as assessed by BICR-confirmed progression-free survival (PFS).

1.2.2 Rationale for Savolitinib in PRCC

This is a Phase III study comparing savolitinib to sunitinib in patients with unresectable and locally advanced, or metastatic PRCC, with or without previous treatment. This trial is justified for the following reasons:

- The relevance of altered MET signalling in RCC and in particular in PRCC has been established. For PRCC, NGS has been able to identify patients with *MET* abnormalities that can be important drivers of the disease, eg, chromosome 7 gain is present in approximately 40% to 75% of patients with PRCC. Preclinical studies have shown that activation of MET signalling promotes angiogenesis and may play a role in adaptive resistance to VEGF blockade.
- Savolitinib monotherapy is capable of inhibiting tumour growth in mouse tumour models harbouring *MET* aberrations in multiple indications.
- A Phase II study of savolitinib has shown preliminary clinical efficacy in patients with MET-driven PRCC. With a short follow-up, approximately 20% of MET-driven patients have shown an objective response at 6 months.
- Based on data from Phase I and II studies, the administration of savolitinib 600 mg/day is generally well tolerated with the majority of events being low grade and with a low incidence of treatment-related withdrawals. As outlined in Section 6.1.1, patients with lower body weights may be at greater risk of hepatotoxicity. Therefore, a 400-mg dose for patients below 50 kg will be used to potentially reduce the risk of hepatotoxicity.

In summary, early evidence of antitumour activity, tolerability, and a clear molecular rationale warrant a Phase III trial of savolitinib to confirm efficacy in a comparative study.

1.2.3 Rationale for sunitinib as comparator

Sunitinib is a multi-kinase VEGF inhibitor approved by the Food and Drug Administration for the treatment of advanced renal-cell carcinoma and is considered a first-line treatment option. The biology of VEGF expression as a result of VHL mutation applies exclusively to clear-cell

RCC, and thus the most robust effects of VEGF-targeting agents are expected in patients with pure clear-cell histology. To date, there are no proven treatments approved specifically for non-clear cell RCC although Phase II studies have shown responses to VEGF TKIs.

Two recent randomised studies in non-clear cell RCC (Armstrong et al 2016, Tannir et al 2015) showed a trend towards better disease control with sunitinib than with everolimus. In the ASPEN study, sunitinib significantly increased PFS compared with everolimus (8.3 months [80% CI 5.8–11.4] vs 5.6 months [5.5–6.0]; hazard ratio 1.41 [80% CI 1.03–1.92]; p=0.16), although heterogeneity of the treatment effect was noted on the basis of histological subtypes and prognostic risk groups. Additionally, in an exploratory, non-powered subset analysis of the ASPEN trial, sunitinib was more effective in prolonging PFS in patients with PRCC (66% of the patient population) than everolimus (8.1 months [80% CI 5.8-11.1] for sunitinib vs. 5.5 months [4.4-5.6] for everolimus).

1.2.4 Rationale for line-agnostic study

Preliminary analysis of the Phase II PRCC study suggests that the main determinant of benefit from savolitinib is MET-driven status. The updated Phase II study data from November 2016 show no apparent difference in PFS between MET-driven first-line patients (N=21) and MET-driven patients who were previously treated (N=23), supporting the line-agnostic design.

1.2.5 Rationale for exclusion of patients with co-occurring *FH/VHL* mutations

Molecular characterisation of PRCC by The Cancer Genome Atlas (TCGA) Research Network (The Cancer Genome Atlas Research Network 2016) has classified PRCC into three molecular subgroups independent of histology. One such group described a CpG island methylator phenotype (CIMP) subtype which was described in 5.6% of PRCC cases. The CIMP subtype is characterised by a mutation of the gene encoding fumarate hydratase (FH). These tumours were associated with the worst overall survival (OS). Germline mutation of *FH* has been observed in the aggressive type 2 tumours associated with the hereditary leiomyomatosis and renal-cell cancer syndrome (Grubb et al 2007). It is not known whether alterations of *FH* or the MET pathway will be the dominant driver in the <6% of PRCC that may harbour both of these pathway alterations.

In the Phase II savolitinib study (clinicaltrials.gov identifier: NCT02127710), no patient with MET-driven PRCC and a co-occurring *FH* mutation experienced clinical benefit from drug treatment. Therefore, the Phase III savolitinib study will exclude patients with co-occurring *FH*- and MET-driven status.

Von Hippel-Lindau (*VHL*) mutation is the hallmark of clear cell renal carcinoma, present in nearly 90% of sporadic clear cell kidney cancers (Linehan et al 2012). Several FDA-approved

agents that target the *VHL* pathway, including sunitinib, have been approved for the treatment of patients with advanced kidney cancer. No patient with MET-driven PRCC in the Phase II savolitinib study was found to have a co-occurring *VHL* mutation. Therefore, the Phase III study will exclude patients with co-occurring *VHL* and MET-driven status.

1.3 Benefit/risk and ethical assessment

Patients with locally advanced or metastatic PRCC have no curative or standard of care treatment options. Standard therapies used to manage patients with renal cell cancer appear to be less effective in patients with PRCC compared to those with clear cell RCC. Aberrant MET activation is prominent in PRCC as a result of *MET* amplification, HGF/MET protein overexpression, *MET* activating mutation or HGF/MET autocrine loops. In addition, trisomy of chromosome 7 (locus of both MET and its ligand HGF) is present in 40% to 75% of patients with PRCC. The Phase II study showed a significant improvement in PFS in MET-driven patients compared to MET-negative patients. No responses have been seen in MET-negative patients. Drug-induced liver injury (DILI) has been identified as a risk for patients receiving savolitinib and requires specific monitoring. Frequent monitoring of liver function tests will take place as outlined in the study plan. The hepatotoxicity management algorithm included in the protocol clearly defines and limits the patients who can be re-challenged to those with lower grade abnormalities with rapid resolution. As stated in the eligibility criteria and risk mitigation sections, patients with abnormal baseline liver function tests will be excluded from the study and patients will be required to discontinue or reduce the dose of statins prior to study entry. Pyrexia and hypersensitivity have been identified as a risk for patients receiving savolitinib. Pyrexia was followed in some cases by drug induced liver injury (see above) or an association of symptoms suggestive of hypersensitivity such as, but not limited to, allergic rash, cytopenia, myalgia/arthralgia [redacted] Patients who experience pyrexia with or without an association of the above symptoms after initiation of savolitinib treatment must follow the toxicity management guidelines. The QTc interval prolongation potential of savolitinib 600mg was assessed in a thorough QT study in healthy volunteers. Analysis of the data concluded that it is a positive study as the upper two-sided 90% CI for the mean placebo-adjusted change from baseline in QTc corrected by Fridericia's method (ΔΔQTcF) was 13.6 and 14.0 msec at 4 and 5 hours, respectively. Regular ECG assessments will be done throughout the study according to the study plan. Patients who present ECG abnormalities with or without symptoms during treatment with savolitinib must follow the QTc prolongation toxicity management guidelines.

The investigation of savolitinib in this patient population appears acceptable based upon the non-clinical safety profile, the emerging clinical safety profile, the risk minimisation and adverse event management strategies, evidence of activity in patients with MET-driven PRCC, the lack of effective alternative treatments and the strength of the scientific hypothesis

under evaluation. Overall the benefit/risk assessment supports the administration of savolitinib in patients with MET-driven PRCC in accordance with this protocol.

1.4 Study design

This is an open-label, randomised, controlled, multicentre, phase III study designed to evaluate the efficacy of savolitinib compared to sunitinib in patients with MET-driven, unresectable and locally advanced, or metastatic PRCC. Patients can be treatment naïve or previously treated but cannot have previously received sunitinib or a MET inhibitor. Patients who have received prior systemic therapy must have had disease progression in soft tissue disease or bone within 6 months of the last dose of the most recent systemic therapy. Bone progression is defined by the appearance of ≥2 new lesions on bone scan. Supportive care agents such as denosumab or radium 223 are not considered prior systemic therapy, and patients who have received these agents are potentially eligible.

Patients must have at least one lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements and Karnofsky Performance Status ≥80.

Once the patient has undergone the Part 1 screening visit and signed the Part 1 ICF, a formalin-fixed and paraffin-embedded (FFPE) tumour sample meeting the requirements specified in the Laboratory Manual will be sent to the sponsor-designated central laboratory. For first-line patients, the diagnostic specimen can be used. For previously treated patients, the most recent archival specimen obtained during a clinical procedure is preferable to the diagnostic specimen only if it meets specifications and has an equal or higher tumour cellularity. If the above is not available or unlikely to yield sufficient material for testing, the patient will have the option to provide an FFPE tumour tissue block from a de-novo core needle tumour biopsy. The biopsied tumour lesion must not be a RECIST target lesion, as the biopsy may affect the accuracy of the imaging.

Locally available pathology results confirming PRCC will be used for study entry. All patients must have a confirmed MET-driven tumour by the sponsor designated central laboratory using Next Generation Sequencing (NGS) to evaluate for qualifying alterations prior to study entry.

A MET-driven tumour is defined as any of the following molecular alterations or combination of these alterations detected in tumour tissue using the validated NGS test in the absence of co-occurring *FH* or *VHL* mutations:

- Chromosome 7 gain.
- *MET* amplification.

- *MET* kinase domain mutations.
- *HGF* amplification.

Absence of co-occurring *VHL* mutation in "MET-driven" tumours is also required as *VHL* mutations are a hallmark of ccRCC.

The main study (Part 2) screening assessments must take place within 28 days of signing the ICF for Part 2. Randomisation must take place within 28 days of signing the ICF for Part 2.

Patients who fulfil all the eligibility criteria will be randomised in a ratio of 1:1 to receive:

- Savolitinib 600 mg (400 mg if <50 kg) by mouth (PO) with a meal once daily (QD)

versus

- Sunitinib 50 mg PO QD, with or w/o food.

For the purposes of planning, a 6-week period will be called a 'cycle'. Treatment with sunitinib will be given 4 weeks on/2 weeks off. Treatment with savolitinib will be given continuously.

Patients will be stratified based on the IMDC risk group criteria (Kroeger et al 2013), using the number of pre-defined risk factors to assign patients into favourable, intermediate or poor prognostic groups as well as whether they are treatment naive or previously treated with or without a VEGF-TKI.

Following randomisation, patients will attend scheduled study visits as outlined in the study Plan (Table 1). Efficacy will be assessed by tumour assessments every 6 weeks, corresponding to the start of each cycle, and then every 12 weeks after the first year, until disease progression as defined by RECIST 1.1 and confirmed by BICR. All scans will be read by BICR after notification of Progressive Disease by the investigator. If PD is not centrally confirmed, each subsequent scan will be read by BICR once it is received and processed by the sponsor-designated vendor (see Section 5.1.3). Depending on the speed and completeness of image submission to the sponsor-designated vendor, the turn-around time generally should be within 10 days.

During verification of the institution's diagnosis of radiographic progression by BICR, participants should continue to receive study treatment if not medically contra-indicated. The decision whether to continue or to withhold study treatment will be at the discretion of the investigator, but if not medically contra-indicated, patients should be strongly encouraged not to start subsequent anti-cancer therapy until BICR-confirmation of PD. If disease progression is not confirmed by BICR, the patient may continue/resume study treatment and must continue to undergo assessments as per Table 1, including tumour evaluations at 6-week intervals (or sooner if felt to be medically indicated) until disease progression is confirmed by

BICR. Those patients who begin subsequent non-study anti-cancer therapy prior to BICR-confirmed PD should continue to undergo tumour assessments, and sites must send each scan to the sponsor-designated vendor until PD is confirmed by BICR.

Regardless of initial treatment, patients will have two options for post-progression therapy following BICR-confirmation of PD:

1 Receive subsequent non-study anti-cancer therapy that does not contravene local practice.
2 Continue to receive the assigned study treatment as long as in the opinion of the investigator, the patient is deriving benefit and the patient meets the original eligibility criteria in terms of Performance Status and laboratory values. This decision must be discussed with and approved by the AstraZeneca study physician. Such patients will continue to undergo monitoring as per the Study Plan (Table 1).

There will be no cross-over.

An EOT visit will be conducted as soon as possible and preferably within 7 days following the decision to discontinue study medication.

The purpose of this visit is to:

(a) discuss any further treatment options and/or follow-up.
(b) discuss the possibility of a biopsy, which should be strongly encouraged, particularly for patients who had responded to treatment (patients may have signed a consent line for this on the Main Study ICF).
(c) obtain the required EOT tests (Table 1) and collect the ePRO device after the last set of questionnaires are completed.
(d) collect any unused study medication and study-medication containers from the patient.

Once a patient permanently discontinues study drug, a 30-day (±7 days) safety follow-up will be performed to follow-up on any SAE/AEs and concomitant medications (including any subsequent cancer therapy). If there are no ongoing SAE/AEs at the time of drug discontinuation, the safety follow-up can be done via telephone contact.

Determination of PD on subsequent anti-cancer therapy in patients who had PD by RECIST 1.1 on study medication (PFS2) will be by institutional call. Patients who choose to continue on their initial therapy after BICR-confirmed PD will not be considered to have a second PFS event until they discontinue study medication and progress on subsequent anti-cancer treatment.

In the OS follow-up period following second progression (PFS2), subsequent therapies and vital status will be documented at least every 12 weeks until death, lost to follow-up, withdrawal of consent, or end of study, whichever comes first.

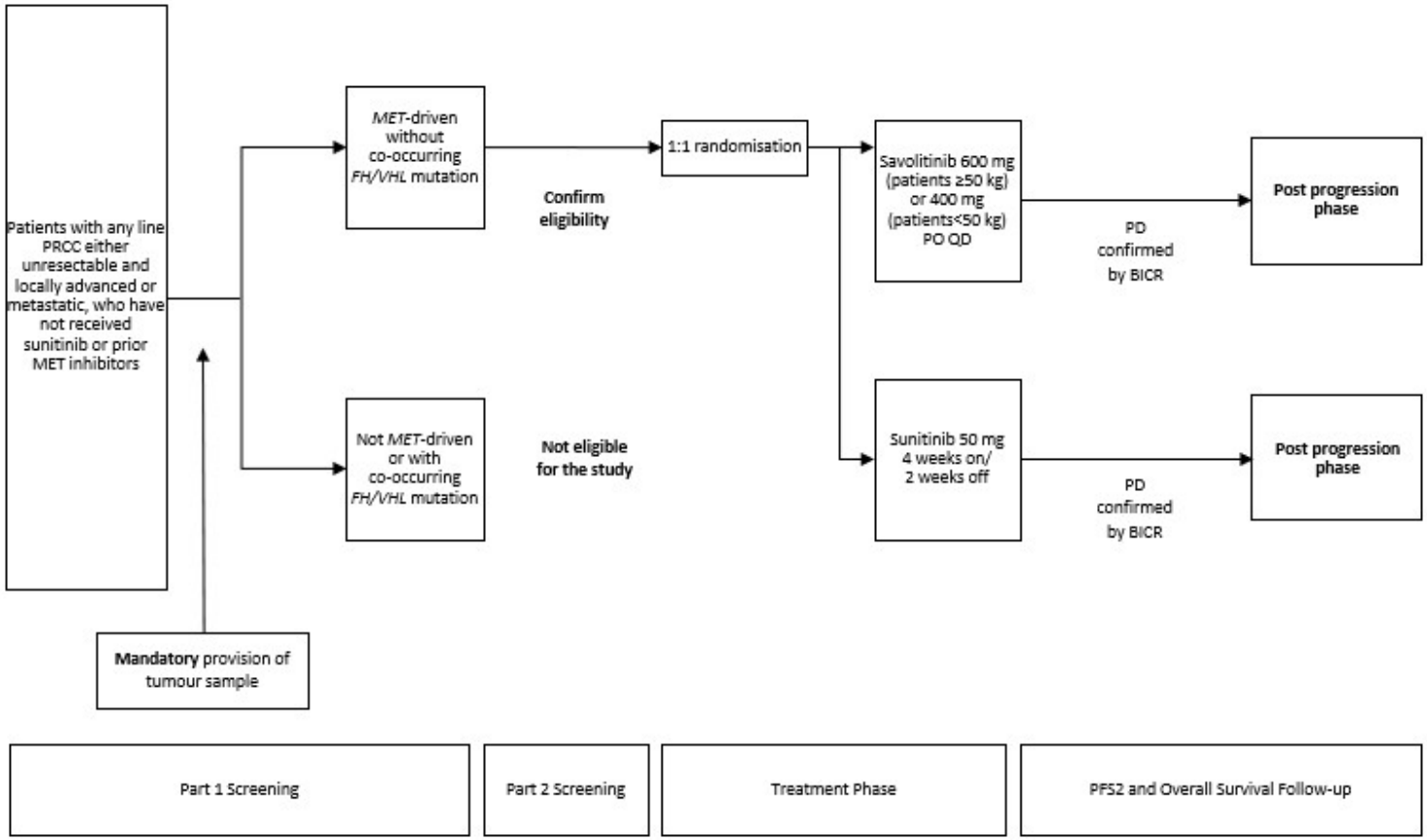
A recent review of the final results of the Molecular Epidemiology Study (MES) concluded that in this data-set, [redacted] It was also concluded that the SAVOIR study design would not benefit from a study size reassessment [redacted]

Following a review of the MES results, a decision, endorsed by the Independent Data Monitoring Committee (IDMC), was made to terminate recruitment into SAVOIR.

Patients randomised in SAVOIR may continue to receive their assigned treatment for as long as they are deriving clinical benefit or until they meet a protocol-defined stopping criterion and must follow the study plan as outlined. Patients already in screening (who have signed the ICF) will have the option to continue screening and to be randomised if eligible.

Further information can be found in Section 4.3.5.

Figure 1 Study flowchart



BICR, Blinded Independent Central Review; *FH/VHL*, fumarate Hydratase/von Hippel-Lindau; PD, progression of disease; PFS2, second progression-free survival; PO, orally; PRCC, papillary cell renal carcinoma; QD, once a day.

1.5 Study governance and oversight

1.5.1 Independent Data Monitoring Committee

This study will use an external IDMC to perform interim reviews of accumulating study safety data. This committee will be composed of therapeutic area experts, including an independent hepatic expert to evaluate potential Hy's law cases, and a statistician, who are not employed by AZ, and do not have any major conflict of interest. Following the review, the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will only include the recommendation and any potential protocol amendments. A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC. The charter will describe the plan to provide safety reports (individual case safety report or serious adverse event report) and follow up safety reports concerning liver dysfunction to the IDMC in real time.

In addition to the periodic review of safety data by an IDMC, the safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the study protocol and letters to investigators. Abnormalities in liver function tests as well as any clinical adverse events associated with liver dysfunction will be reported quarterly to the FDA.

Following IDMC endorsement to terminate recruitment into SAVOIR, the interim analysis will not occur. However, interim reviews of safety data by the IDMC will continue until end of study. Further statistical information can be found in Section 8.1.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary objective:	Outcome measure:
To determine the efficacy of savolitinib when compared to sunitinib in patients with MET-driven, unresectable and locally advanced, or metastatic PRCC	• PFS (time to earliest progression as defined by RECIST 1.1 and confirmed by BICR, or death)

2.2 Secondary objectives

Secondary objective:	Outcome measure:
To compare the efficacy of savolitinib versus sunitinib in patients with MET-driven, unresectable and locally advanced, or metastatic papillary renal cell carcinoma (PRCC)	• Overall Survival (OS) • Objective Response Rate (ORR), duration of response (DoR) and best percentage change in tumour size by BICR using RECIST 1.1 criteria • Disease Control Rate (DCR) at 6 and 12 months
To assess the impact of savolitinib and sunitinib on disease related symptoms and health-related QOL in this patient population	• Mean change from baseline in FKSI-19 and FACIT-F scores
To evaluate the pharmacokinetics of savolitinib in this patient population	• PK concentration data

2.3 Safety objectives

Safety objective:	Outcome measure:
To evaluate the safety and tolerability of savolitinib in relation to sunitinib	• AEs/SAEs adverse events [AEs] as characterised and graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Event [CTCAE], collection of clinical chemistry/haematology parameters, liver function tests, echocardiograms and electrocardiograms (ECGs), vital signs including blood pressure (BP) and heart rate

2.4 Exploratory objectives

Exploratory objective:	Outcome measure:
To compare the efficacy of savolitinib versus sunitinib in patients with MET-driven, unresectable and locally advanced, or metastatic papillary renal cell carcinoma PRCC	• Time from randomisation to objective disease progression on subsequent anti-cancer therapy after PD by RECIST 1.1 on study medication, or death (PFS2)
To assess the impact of savolitinib vs. sunitinib on patient reported AEs	• Collection of PRO CTCAE symptoms

Exploratory objective:	Outcome measure:
To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason for hospitalisations and unscheduled clinic visits, procedures undertaken and length of hospital inpatient stays • Health state response and utility index derived from the EQ-5D-5L
[redacted]	[redacted]
To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study medications and or susceptibility to disease (optional)	• Pharmacogenetic analyses on blood samples
[redacted]	[redacted]

The exploratory analyses may not be reported in the clinical study report (CSR). They may be reported separately and may also form part of a pooled analysis with other studies.

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

The patient population should be selected without bias. Investigator(s) should keep a record of the patient screening log for both Part 1 and Part 2. Determination of MET-driven status at any laboratory other than the sponsor-designated central laboratory will not be permitted.

3.1 Inclusion criteria

***** After signing the Part 1 ICF, patients will undergo eligibility review of the asterisked criteria and after signing the Main Study (Part 2) ICF, patients will undergo eligibility review of all inclusion/exclusion criteria below.

For inclusion in the study patients should fulfil the following criteria:

1 Provision of informed consent prior to any study specific procedures, sampling and analyses.*

2 Females and/or males age ≥18 years.*

3 Histologically confirmed PRCC, which is unresectable and locally advanced, or metastatic*. Patients with minor clear cell components (<50%) are permitted, provided that the dominant and presumed primary histology is papillary. Patients with papillary urothelial carcinoma or renal pelvis cancer of the kidney are not considered PRCC and are not eligible.

4 Patients who have received no prior systemic therapy as well as those who have received prior systemic therapy for PRCC in the advanced setting.* Patients can be treatment-naïve, or previously treated, but cannot have previously received sunitinib or a MET inhibitor. Patients who have received prior systemic therapy must have had disease progression in soft tissue disease or bone within 6 months of the last dose of the most recent systemic therapy. See Section 1.4.

5 Confirmation of MET-driven PRCC without co-occurring *FH* or *VHL* mutations from an FFPE tumour sample using the sponsor-designated central laboratory validated NGS assay.

6 Karnofsky performance status ≥80.

7 Patients must have measurable disease on the baseline scan as per RECIST 1.1 (see Appendix F). The main target lesion should preferably not have been used for a biopsy within 4 weeks of randomisation.

8 Adequate haematological function, defined as:

- Absolute neutrophil count (ANC) ≥1500/μL
- Haemoglobin (Hgb) ≥9 g/dL (no transfusion in the past 2 weeks)
- Platelets ≥100,000/μL (no transfusion in the past 10 days)

9 Adequate liver function defined as:

- ALT and AST ≤2.5 x the upper limit of normal (ULN) with total bilirubin (TBL) ≤1x ULN

OR

- TBL >1xULN-≤1.5x ULN with ALT and AST ≤1x ULN

10 Adequate renal function defined as a creatinine <2 times the institutional upper limit of normal OR a glomerular filtration rate (GFR) ≥30 mL/min, as assessed using the standard methodology at the investigating centre (eg, Cockcroft-Gault, MDRD or CKD-EPI formulae, EDTA clearance or 24-hour urine collection).

11 Adequate coagulation parameters defined as International Normalisation Ratio (INR) and activated partial thromboplastin time (aPTT) <1.5 x ULN, unless patients are receiving therapeutic anti-coagulation which affects these parameters.

12 Adequate cardiac function defined as an ejection fraction (EF) of ≥50%.

13 Patients with known tumour thrombus or deep vein thrombosis (DVT) are eligible if clinically stable on anticoagulation for ≥2 weeks.

14 Females should be using adequate contraceptive measures, should not be breast feeding, and must have a negative pregnancy test if of childbearing potential, or must have evidence of non-childbearing potential by fulfilling one of the following criteria:

- Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
- Women under the age of 50 years would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution.

15 Male patients with female partners of child-bearing potential should be willing to use barrier contraception, ie, condoms, during the study and for 6 months following discontinuation of study drug.

16 Ability to swallow and retain oral medications.

17 Willingness and ability to comply with study and follow-up procedures*.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)*.

2 Previous randomisation on the present study*.

3 Most recent cytotoxic chemotherapy, immunotherapy, chemo-immunotherapy, or investigational agents <28 days from the date of randomisation. Most recent non-cytotoxic targeted therapy <14 days from the date of randomisation.

4 Unresolved toxicities from any prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 on the date of randomisation with the exception of alopecia.

5 Prior treatment with a MET inhibitor (eg, foretinib, crizotinib, cabozantinib, onartuzumab or previous savolitinib) or sunitinib.*

6 Treatment with strong inducers or inhibitors of CYP3A4 or strong inhibitors of CYP1A2, taken within 2 weeks or not possible to be stopped for at least 2 weeks before the date of randomisation. Herbal medications cannot be taken within 7 days of the date of randomisation (3 weeks for St John's wort). See Appendix H.

7 Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to the date of randomisation or has not recovered from side effects of such therapy.

8 Major surgical procedures ≤28 days of randomisation or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement.

9 Untreated brain metastases or if treated, radiation or surgery must have been completed at least 2 weeks prior to the main study screening visit, without evidence of central nervous system disease progression, patients must be neurologically stable with no more than mild neurologic symptoms, and without requirement for chronic corticosteroid therapy to control symptoms.

10 Current leptomeningeal metastases or spinal cord compression due to disease*.

11 History of serious liver disease, with or without normal LFTs, such as cirrhosis, Wilson's disease*.

12 Active hepatitis B (positive HBV surface antigen (HBsAg) result) or hepatitis C (HCV). Patients with a past or resolved HBV infection are eligible* if:

- negative for HBsAg and positive for hepatitis B core antibody [anti-HBc] or
- positive for HBsAg but for >6 months have had normal transaminases and HBV DNA levels between 0 – 2000 IU/ml (inactive carrier state) and willing to start and maintain antiviral treatment for at least the duration of the study
- HBV DNA levels >2000 IU/ml but on prophylactic antiviral treatment for the prior 3 months and will maintain the antiviral treatment during the study

Patients with positive HCV antibody are eligible only if the qualitative polymerase chain reaction test is negative for HCV RNA.

13 Acute or chronic non-diabetic pancreatic insufficiency or inflammation*.

14 Active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (eg, ulcerative disease, uncontrolled nausea, vomiting, diarrhoea Grade ≥2, and malabsorption syndrome).

15 Uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy).

16 Any clinically important abnormalities in rhythm, conduction or morphology of resting electrocardiograms (ECGs), including but not limited to complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250 msec.

17 Mean resting QTcF >470 msec for women and >450 msec for men on the Part 2 screening triplicate ECGs or factors that may increase the risk of QTcF prolongation such as chronic hypokalaemia not correctable with supplements, congenital or familial long QT syndrome, or family history of unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes (Appendix I).

18 Any of the following cardiac diseases within the last 6 months:

- Unstable angina pectoris
- Congestive heart failure (New York Heart Association [NYHA] ≥ Grade 2 (Appendix K)
- Acute myocardial infarction
- Stroke or transient ischemic attack

19 Serious underlying medical condition at the time of treatment that would impair the ability of the patient to receive protocol treatment.

20 Known serious active infection including, but not limited to, tuberculosis, or human immunodeficiency virus (positive HIV 1/2 antibodies).

21 Presence of other active cancers, or history of treatment for invasive cancer, within the last 5 years. Patients with Stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients

with previously treated in situ carcinoma (ie, non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

22 Women who are either pregnant or breast-feeding.

23 Known hypersensitivity to the active or inactive excipients of savolitinib or sunitinib.

24 Presence of non-healing wounds.

25 Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements*.

For procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

Investigator(s) should keep a record, the subject screening log, of patients who entered Part 1 screening.

The investigator(s) will:

1 Obtain a signed Part 1 ICF from the potential patient before any study specific procedures are performed.

2 Assign the potential patient a unique enrolment number, beginning with 'E#'.

3 Determine patient eligibility (please see asterisked criteria in sections 3.1 and 3.2)

4 Obtain signed main study (Part 2) ICF from the potential patient before any Part 2 screening procedures are performed.

5 Determine patient eligibility. See Section 3.

6 Upon confirmation of eligibility, randomise the patient using the randomisation system which is available for this trial, answering all questions which are asked by the system including questions relative to the stratification factors.

7 The randomisation system will randomly assign treatment (savolitinib or sunitinib) and this information will be made available to the site personnel.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the investigator (or nominated assistant) should contact the IVRS/IWRS Centralised Randomisation Centre for allocation of randomised therapy. Patients will be identified to the Centralised Randomisation Centre using patient E-code and date of birth. The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the IVRS/IWRS database. The randomisation scheme will be produced by a computer software program called AZRand (AZ Randomisation system) that incorporates a standard procedure for generating random numbers.

A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group. The randomisation scheme will be stratified (See Section 3.5) based on:

- IMDC risk categorisation (favourable, intermediate, poor prognosis)
- Treatment naïve versus previously treated with or without a VEGF-TKI.

Every effort should be made to minimise the time between enrolment and starting treatment.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Eligible patients will be randomised in a 1:1 ratio. The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the Interactive Voice Response System / Interactive Web Response System (IVRS/IWRS) database.

Patients will be stratified based on the IMDC risk group criteria (Kroeger et al 2013), using the number of predefined risk factors to assign patients into favourable, intermediate, or poor prognostic groups as well as whether they are treatment naïve versus previously treated with or without a VEGF-TKI. The VEGF-TKIs that are currently most used in PRCC treatment include sunitinib, bevacizumab, cabozantinib, pazopanib, axitinib, sorafenib, and lenvatinib (in combination with everolimus).

The IMDC model includes the following 6 independent predictors of poor survival at study entry: Karnofsky performance status <80%, interval from initial diagnosis to first systemic treatment <1 year, haemoglobin <LLN, corrected calcium >ULN, absolute neutrophil count >ULN, and platelet count >ULN. According to the number of poor prognostic factors, patients are segregated into favourable (0 factors), intermediate (1 to 2 factors), and poor

(≥3 factors) risk groups. Based on these stratification criteria, patients will be stratified to 1 of the following 9 strata:

- Treatment naïve, favourable prognosis.
- Treatment naïve, intermediate prognosis.
- Treatment naïve, poor prognosis.
- Previous treatment not including a VEGF TKI, favourable prognosis.
- Previous treatment not including a VEGF TKI, intermediate prognosis.
- Previous treatment not including a VEGF TKI, poor prognosis.
- Previous treatment with a VEGF TKI, favourable prognosis.
- Previous treatment with a VEGF TKI, intermediate prognosis.
- Previous treatment with a VEGF TKI, poor prognosis.

Specific information concerning the use of IVRS/IWRS will be provided in a separate manual.

It is recommended that patients commence study treatment on the day of randomisation if possible, and if not, then ideally within 3 days.

3.6 Restrictions

3.6.1 Need for contraception

There are no studies in pregnant women taking savolitinib or sunitinib. However, studies in animals have shown that either drug may cause harm to a foetus. Patients of child bearing potential and their partners who are sexually active, must agree to the use of highly effective forms of contraception while taking study medication. Female patients on savolitinib must continue to use contraception for 1 month after their last dose. Acceptable methods of contraception include full abstinence, tubal ligation, combined oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (eg, Depo-Provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems, and vasectomised partners. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

Studies in animals taking savolitinib have shown some abnormalities in sperm development. Therefore, male patients must use a condom during sexual intercourse with a female partner of childbearing potential (pregnant or not) and refrain from donating sperm during the study and for 6 months after their last dose. For details refer to Appendix D “Acceptable Birth Control Methods”.

3.6.2 Prohibited concomitant medications and treatments

No other investigational therapy should be given to patients. No anticancer agents should be given to patients other than the study medications. If such agents are required for a patient, then the patient must first be withdrawn from the study.

Herbal preparations/medicines

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to the date of randomisation (3 weeks for St John's wort).

Statins

For patients on savolitinib, discontinuation of statins is advised unless considered essential, in which case, the patients should be prescribed the lowest available dose and monitored for the effects of increased statin exposure.

Acetaminophen (Paracetamol)

The administration of acetaminophen (paracetamol) is restricted to 3 grams per day, or the maximum dose approved locally (if less than 3 grams per day) during the study. In the event of an elevation in hepatic transaminases or bilirubin, the use of acetaminophen should be avoided until resolution of the affected parameter.

Drugs that prolong QT interval

The concomitant administration of drugs known to prolong QT interval is restricted unless considered essential due to patient management, in which case, patients should be closely monitored with more frequent ECGs. Additional guidance on drugs known to prolong QT interval is provided in Appendix I.

Food restrictions

Patients should abstain from eating grapefruit and Seville oranges (and other products containing these fruits, eg, grapefruit juice or marmalade) during the study.

UV exposure

During savolitinib therapy and for 4 weeks after the last dose, patients should be advised to avoid prolonged exposure to the sun, wear protective clothing, a hat and seek shade from the sun as far as possible; in addition, SPF30+ sunscreen should be used. Exposure to other sources of UV light including sunbeds and tanning booths, etc. should be avoided.

3.7 Post-progression therapy

Regardless of initial treatment, patients will have two options for post-progression therapy following BICR-confirmation of PD:

1 Receive subsequent non-study anti-cancer therapy that does not contravene local practice.
2 Continue to receive the assigned study treatment as long as in the opinion of the investigator, the patient is deriving benefit, and the patient meets the original eligibility criteria in terms of performance status and laboratory values. This decision must be discussed with and approved by the AstraZeneca study physician. Such patients will continue to undergo monitoring as per the Study Plan (Table 1) while on study treatment.

There will be no cross-over.

3.8 Discontinuation of investigational product

Patients may be discontinued from savolitinib or sunitinib in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event as per study criteria.
- Pregnancy.
- Severe non-compliance with the Clinical Study Protocol.
- BICR-confirmed PD unless the physician feels that the patient is still deriving benefit from the initial treatment and confirms that the patient meets the original eligibility criteria in terms of performance status and laboratory values. This must be discussed with and approved by the AstraZeneca study physician.
- Patients was incorrectly initiated on investigational product (Section 3.4).
- The investigator decides the patient should not be continued on the trial/is no longer deriving benefit from the study medication.

After discontinuation of the study treatment at any point in the study, all ongoing AEs or SAEs must be followed until resolution or until the event becomes stable (or returns to baseline) unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Section 6.3.2). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study treatment must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4) and followed to resolution or until the event becomes stable (or returns to baseline) or is unlikely to resolve further in the opinion of the investigator. Patients should be contacted or seen 30 days (±7 days) after discontinuing the last dose of study medication to collect and /or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study medication should also be reported as an AE.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Any patient who has not yet shown BICR-confirmed PD at discontinuation of study medication should continue to be followed with centrally reviewed scans until there is BICR-confirmation of PD, regardless of whether subsequent anti-cancer therapy is started.

3.8.1 Procedures for discontinuation of a patient from study treatment prior to BICR-confirmed PD

Patients who discontinue study-medication prior to BICR-confirmed PD will be asked about the reason(s) for discontinuation and the presence of any AEs. In addition, the date of discontinuation, the reason and any medications taken at the time of discontinuation will be recorded on the eCRF. If a patient discontinues study treatment, the study monitor must be informed immediately.

If the reason for study medication discontinuation is due to investigator-assessment of PD using RECIST 1.1 (but prior to BICR confirmation due to delay or a BICR discrepancy), patients should be encouraged, if not medically contraindicated, to not start subsequent anti-cancer therapy and continue to undergo disease assessments until BICR-confirmed PD. Once there is BICR-confirmed PD, patients will be followed for PFS2 and OS as per Sections 4.3.3 and 4.3.4.

However, if this is not an option for the patient and/or physician, or if the study medication was discontinued for any other reason other than PD, then an EOT visit will be conducted as soon as possible and preferably within 7 days following the decision to discontinue study medication.

The purpose of this visit for patients who discontinue study-drug prior to BICR-confirmed PD is to:

(a) discuss any additional treatment options and follow-up.
(b) discuss the possibility of a biopsy, which should be strongly encouraged, particularly for patients who had responded to treatment (patients may have signed a consent line for this on the Main Study ICF).
(c) obtain the required EOT tests (Table 1) and collect the ePRO device after the last set of questionnaires are completed.
(d) collect any unused study medication and study-medication containers from the patient.

By discontinuing study treatment, the patient is not withdrawn from the study. If a patient decides to voluntarily withdraw (ie, patient choice), then the Withdrawal ICF (Informed Consent Form Addendum – Options for Withdrawal of Consent) should be used to determine

if they are willing to undergo follow-up. Section 3.9.2 outlines the criteria for withdrawal from study.

3.9 Criteria for withdrawal from the study

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study without prejudice to further treatment.
- Incorrectly enrolled patients ie, the patient does not meet the required inclusion/exclusion criteria for the study. This option is only applicable to patients not randomised into the study (ie, screen failures identified prior to randomisation).

If a patient voluntarily withdraws consent, they will fill out the Withdrawal ICF (Informed Consent Form Addendum – Options for Withdrawal of Consent) and be specifically asked if they are withdrawing consent for further follow-up, eg, survival calls.

3.9.1 Screen failures

Screen failures are patients who either are not MET-driven (Part 1 screen failures), and therefore cannot go on to the main study (Part 2) screening, or who do not fulfil the eligibility criteria for the main study (Part 2 screen failures), and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as "Screen failure" (ie, the potential patient does not meet one or more of the required inclusion/exclusion criteria) in IVRS/IWRS). 'Failure to meet randomisation criteria' should be selected for situations where the patient has been unable to fulfil/satisfy the main study (Part 2) criteria required for assignment into a randomised group.

3.9.2 Withdrawal of the informed consent

Patients are at any time free to withdraw from the study (study medication and assessments), without prejudice to further treatment. Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.3.2 and Section 4.3.2). All study medication and empty study medication bottles should be returned by the patient as well as the electronic PRO (ePRO) devices.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused.

In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3.10 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant.
- are assessed as causally related to study medication.
- are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study schedule: Screening, On Study Treatment, Discontinuation and Follow-up

	Part 1 Screening Visit	Part 2 Screening Visit[2]	Cycle 1						Cycle 2						Cycle 3 & beyond (every 6 weeks)	EOT[18]	Safety Follow-up[19]	PFS2[32]	Overall Survival Follow-Up[20]
			D 1	D 8	D 15	D 22	D 29	D 36	D 1	D 8	D 15	D 22	D 29	D 36	D1				
Site Visit	0	1	**2**		**3**		**4**		**5**		**6**				**7**				
Day		-28 to 0	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**				
Activity Visit Window			0	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 7d				
Part 1 Screening Informed Consent Form[1]	X																		
Demography, medical/surgical history[3]	X																		
Cancer therapy[4]	X															X	X	X	X
FFPE tumour sample for MET-driven status[6]	X																		
[redacted]	X																		
Main Study (Part 2) Informed Consent Form[1]		X																	
Physical examination		X	X		X		X		X		X				X	X*	X[27]		
Body weight[25]		X	X						X						X				
Vital signs[5]		X	X		X		X		X		X				X	X*	X[27]		

Table 1 Study schedule: Screening, On Study Treatment, Discontinuation and Follow-up

	Part 1 Screening Visit	Part 2 Screening Visit[2]	Cycle 1						Cycle 2						Cycle 3 & beyond (every 6 weeks)	EOT[18]	Safety Follow-up[19]	PFS2[32]	Overall Survival Follow-Up[20]
			D 1	D 8	D 15	D 22	D 29	D 36	D 1	D 8	D 15	D 22	D 29	D 36	D1				
Site Visit	0	1	**2**		**3**		**4**		**5**		**6**				**7**				
Day		-28 to 0	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**				
Activity Visit Window			0	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 7d				
Tumour Assessment[16]		X							X						X			X(by institutional call)	
Karnofsky Performance Status		X	X						X						X	X*			
Smoking Status (Y/N)[24]		X																	
Haematology		X	X		X		X		X		X				X	X*	X[27]		
Clinical Chemistries[29]		X	X		X		X		X		X				X	X*	X[27]		
Corrected calcium[31]		X																	
Liver function tests[21]		X	X	X	X	X	X	X	X	X	X				X	X*	X[27]		
Hepatitis serology[30]		X																	
Coagulation[7]		X[7]																	
Urinalysis[8]		X			X		X		X		X				X		X[27]		

Table 1 Study schedule: Screening, On Study Treatment, Discontinuation and Follow-up

	Part 1 Screening Visit	Part 2 Screening Visit[2]	Cycle 1						Cycle 2						Cycle 3 & beyond (every 6 weeks)	EOT[18]	Safety Follow-up[19]	PFS2[32]	Overall Survival Follow-Up[20]
			D 1	D 8	D 15	D 22	D 29	D 36	D 1	D 8	D 15	D 22	D 29	D 36	D1				
Site Visit	0	1	**2**		**3**		**4**		**5**		**6**				**7**				
Day		-28 to 0	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**				
Activity Visit Window			0	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 7d				
Thyroid Function tests, LDH		X							X						X				
Pregnancy test[9]		X	X						X						X	X			
Triplicate ECGs[10]		X	X	X	X	X	X	X	X						X	X			
Echocardio-gram/MUGA[10]		X		Every 12 weeks (±2 weeks) relative to first dose ◄——►												X			
Prophylactic dental exam[12]		X																	
Pharmacogenetic sample[11]			X																
PK blood collection[13]			X		X		X				X								
[redacted]		X	X						X						X	X			
[redacted]		X	X						X							X			

Table 1 Study schedule: Screening, On Study Treatment, Discontinuation and Follow-up

	Part 1 Screening Visit	Part 2 Screening Visit[2]	Cycle 1						Cycle 2						Cycle 3 & beyond (every 6 weeks)	EOT[18]	Safety Follow-up[19]	PFS2[32]	Overall Survival Follow-Up[20]
			D 1	D 8	D 15	D 22	D 29	D 36	D 1	D 8	D 15	D 22	D 29	D 36	D1				
Site Visit	0	1	**2**		**3**		**4**		**5**		**6**				**7**				
Day		-28 to 0	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**				
Activity Visit Window			0	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 7d				
FACIT-F and PRO CTCAE[17]			X	Bi-Weekly for the first 18 weeks relative to the first dose, then every 4 weeks until EOT visit												X			
EQ-5D-5L and FKSI-19[17]			X	Every 4 weeks until EOT visit												X			
Hospital Resource Use[17]			X			X			X						X		X		
Concomitant Medications		X	X		X		X		X						X	X			
Adverse Events[23]		X	continuously ← →														X		
Drug Dispensing/ Return[33]			X						X						X	X (return only)			
IVRS/IWRS transactions[22]	X	X	X						X						X	X			
Tumour biopsy at relapse[28]																X			

[1] Written informed consent must be obtained before any Part 1 or Part 2 screening activities occur.

[2] Part 2 screening assessments must take place within 28 days of signing the ICF for Part 2. Assessments obtained outside of the 28-day window must be repeated before Cycle 1 Day 1.

[3] Demographic information (age, sex, race, and ethnicity) and a complete medical and surgical history on all (both MET-driven and MET-negative) patients will be collected and recorded in the appropriate eCRFs at the Part 1 screening visit. The medical history will include smoking history in pack years

[4] All previous cancer treatments, including line of therapy, dates of administration, and best response to treatment on all (both MET-driven and MET-negative) patients will be collected and recorded in the appropriate eCRF at the Part 1 screening visit. During follow-up, cancer treatments administered since discontinuing study treatment will be collected.

[5] Vital signs include: heart rate, systolic and diastolic blood pressure, height [only at the main study screening] and temperature.

[6] FFPE tumour sample(s) that meet the specifications in the Laboratory Manual will be analysed prospectively by the sponsor-designated central laboratory by NGS for MET-driven status prospectively, or after study entry in cases where a pre-existing "MET-driven" result is available. See Section 1.4 for qualifying MET-driven alterations.

[7] If INR and aPTT are normal at baseline, they do not need to be repeated unless clinically indicated during the study. Patients on anti-coagulant therapy should have coagulation testing performed according to standard management guidelines.

[8] Urinalysis: If 3+ or greater proteinuria is identified by dipstick assessment, a 24-hour urine collection for formal quantification of the level of protein excretion should be performed.

[9] Women of childbearing potential will have a serum or urine pregnancy test done at main study screening pre-dose Cycle 1 Day 1, on Day 1 of each subsequent cycle, and at treatment discontinuation.

[10] Triplicate ECGs will be performed during the main study (Part 2) screening period, every week in the first cycle, every cycle thereafter, at the end of treatment visit if not done within the last 6 weeks, and at other times if clinically indicated. Echocardiogram/MUGAs will be performed during the main study (Part 2) screening period, every 12 weeks (±2 weeks) relative to the first dose of study medication, at the end of treatment visit if not done within the last 6 weeks, and at other times if clinically indicated.

[11] A 10-mL blood sample for [redacted] will be obtained from the patient pre-dose on 1 Day 1 ([redacted] If for any reason the sample is not drawn prior to dosing it may be collected as soon as possible thereafter. Only one sample will be collected. See Section 5.6.

[12] Patients who have ever received bisphosphonates should undergo a maxillofacial exam during the main study (Part 2) screening period with treatment of active infection and prophylactic treatment of any sites that are at high risk for infection.

[13] Blood sample (2 mL) to be collected from patients assigned to savolitinib pre-dose on Day 1 of Cycle 1, pre-dose and 1 and 3 hours post dosing on Day 15 of Cycle 1, and pre-dose on Day 29 of Cycle 1 and on Day 57 (ie, Day 15 of Cycle 2). The date/time of the last two doses prior to the pre-dose PK samples (should be confirmed in the patient diary) and the date/time the PK sample was drawn and the dose/time the savolitinib is given on the PK day need to be recorded in the eCRF.

[14] [redacted] (10 mL whole blood) will be collected at the Part 2 screening visit and pre-dose Cycle 1 Day 1, and on the same day as each tumour evaluation (including unscheduled evaluations), corresponding to at least every 6 weeks during the first year and 12 weeks thereafter, and at EOT, regardless of whether a sample was just collected at the last scan (see Section 5.7.5).

[15] A [redacted] (10 mL whole blood) will be collected at the Part 2 screening visit, pre-dose Day 1, Cycle 1, at the time of the first tumour evaluation (Cycle 2, Day 1) and at EOT (please see Section 5.7.6).

[16] Baseline tumour imaging studies will be performed within 28 days prior to the date of randomisation and will be repeated every 6 weeks (±1 week), corresponding to the start of each cycle during the first year and then every 12 weeks (±1 week) thereafter, until BICR-confirmed PD using RECIST 1.1.

[17] All PRO (FACIT-F, FKSI-19, PROCTCAE and EQ-5D-5L) questionnaires should be completed using the e-PRO device on the schedule above. The site should check the PRO data and patient compliance on the web-based portal at every clinic visit. All four questionnaires need to be completed at the EOT visit prior to the patient meeting with the physician and then the e-PRO devices should be collected. See section 5.3.2 for hospital resource use, which should be completed using the HOSPAD module on a continuous basis until the Safety Follow-up.

[18] See Section 4.3.1. The asterisked assessments* do not need to be repeated if done within the last 2 weeks and there is no need for follow-up of toxicity. An ECHO/triplicate ECGs need to be performed if not done within the last 6 weeks. [redacted] and a pregnancy test need to be performed. The ePRO device and all unused study medication and study medication bottles should be returned.

[19] A safety follow-up will be performed 30 (±7) days after discontinuation of study medication, to follow-up on any SAE/AE's and record any subsequent cancer therapy. If there are no ongoing SAE/AEs at the time of drug discontinuation, the safety follow-up can be done via telephone contact.

[20] All subsequent anti-cancer therapies and OS status will be documented at least every 12 weeks until death, loss to follow-up, withdrawal of consent, or end of study, whichever comes first.

[21] Blood liver functions (AST, ALT, alkaline phosphatase and total bilirubin) will be monitored weekly x 9 and then at the start of each cycle. In some situations, blood for LFTs may be drawn at a local lab on the days when there is no scheduled clinic visit although the results must be faxed to the treating institution immediately so they can be evaluated in light of the hepatotoxicity algorithm (Section 6.8.1.2 for savolitinib and Section 6.8.2 for sunitinib) and entered into the database.

[22] An IVRS/IWRS transaction needs to be done at every dispensing visit at the start of each cycle. Additionally, every dose reduction needs to be recorded in IVRS/IWRS.

[23] Please see section 6.3. From the part 1 screening visit until the part 2 screening visit, only SAEs related to study procedures must be reported (AEs do not require reporting). From the main study screening (Part 2) onwards, all AEs/SAEs must be reported

[24] Smoking status (Yes (current smoker) /No (not currently smoking) will be recorded at the time of the main study screening (Part 2) visit.

[25] Body weight will be assessed every cycle, and more frequently if clinically indicated. The dose of savolitinib will not change for patients who started the study at <50 kg (ie, 400 mg), even if their weight increases to ≥50 kg during the course of the study.

[26] 20 mL for [redacted] at the Part 1 screening visit only (see Section 5.7.4)

[27] Only necessary if there are ongoing toxicities

[28] A tumour biopsy after treatment discontinuation should be strongly encouraged regardless of treatment arm, particularly for patients who had responded to treatment. See section 5.7.7.

[29] See Table 2 (Section 5.2.1) for list of chemistry evaluations

[30] Hepatitis serology includes HBsAg, anti-HBc (qualitative), HBV DNA, HCV antibody, HCV RNA (if HCV antibody is positive)

[31] To be used for determination of IMDC risk category. Corrected calcium = total calcium (mg/dL) − 0.707 [albumin (g/dL) − 3.4]

[32] Patients will enter the PFS2 follow-up period once the patient has discontinued study medication due to PD by RECIST 1.1. Patients will be followed at least every 12 weeks by site personnel for second progression on subsequent anti-cancer therapy and documentation of all subsequent therapy.

[33] The number of remaining pills at the end of each cycle should be recorded in RAVE. Additionally, patients must bring their medication bottles or blister packs and all remaining tablets or capsules to each clinic visit so that a medication count and reconciliation can be done in conjunction with the medication diary as well as to ensure that the patient has sufficient medication remaining until the next visit. The results of the medication counts and reconciliation should be recorded on IP Accountability logs.

4.1 Screening/enrolment period

Patients will be required to sign a written Part 1 screening ICF for prospective analysis of the MET-driven status using a tumour sample by SAVOIR Clinical Trial NGS assay performed in sponsor designated central laboratory. If this tumour analysis, or a pre-existing MET-driven commercial NGS assay result from the same laboratory, shows that the tumour is MET-driven, patients will be asked to provide informed consent for the main study (Part 2 ICF) prior to starting any additional screening procedures. At the Part 1 screening visit, each potential patient is assigned a unique enrolment code. If a patient withdraws from the study, then the enrolment code cannot be reused.

A pre-existing MET-driven result from a commercial assay from the sponsor designated central laboratory can be used to trigger patient informed consent and entry into the main study, if available. However, a tumour sample from all patients is required for central confirmation of MET-driven tumour status using the SAVOIR Clinical Trial NGS assay.

Demographic data and other characteristics will be recorded and will include: age, gender, race and ethnicity according to local regulations.

A complete medical, surgical and prior anticancer therapy history will be obtained during screening. The medical history is to include smoking history in pack-years. The prior anticancer therapy history is to include all previous treatments (eg, targeted therapy, immunotherapy, cytotoxic chemotherapy, non-TKI anti-angiogenic therapy or combination therapies), line of therapy for each drug or combination, start and stop dates of administration, best response to treatment and reason for discontinuing each drug.

Each patient will undergo the appropriate screening studies as per the study plan (Table 1), either during the Part 1 screening period or to confirm eligibility for the main study during the Part 2 screening within 28 days of signing the ICF for Part 2 (see Sections 3.1 and 3.2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the date of randomisation.

4.2 Treatment period

Evaluations during the treatment period will be performed as detailed in the Study Plan (Table 1).

4.3 Post study-drug follow up

4.3.1 End of Treatment (EOT)

An EOT visit will be conducted as soon as possible and preferably within 7 days following the decision to discontinue study medication.

The purpose of this visit is to:

(a) discuss any further treatment options and/or follow-up.
(b) discuss the possibility of a biopsy, which should be strongly encouraged, particularly for patients who had responded to treatment (patients may have signed a consent line for this on the Main Study ICF).
(c) obtain the required EOT tests (Table 1) and collect the ePRO device after the last set of questionnaires are completed.
(d) collect any unused study medication and study medication containers from the patient.

Standard laboratory tests, physical exam, vital signs and Karnofsky Performance Status do not need to be repeated if done within the last two weeks. An ECHO/MUGA and triplicate ECGs need to be performed if not done within the last 6 weeks. Blood for [redacted] and a pregnancy test need to be performed at the EOT visit. The ePRO device as well as any remaining study medication and study medication containers should be returned.

4.3.2 Safety follow-up

If there are no ongoing SAE/AEs at the time of study medication discontinuation, the safety follow-up with the patient 30 (±7) days after discontinuation of study medication can be done through telephone contact, capturing any new SAEs/AEs and concomitant meds including new therapy. The primary purpose is to follow-up any AEs ongoing at the time of discontinuation and to assess any new AEs that may have occurred since discontinuation. Any AE/ SAE/ abnormal laboratory findings that are ongoing at the time of study treatment discontinuation or any new treatment related events within 30 days of the last study treatment must be followed up to resolution or until the event becomes stable (or returns to baseline) or is unlikely to resolve further in the opinion of the investigator.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

4.3.3 Follow-up for second progression on subsequent anti-cancer therapy after PD by RECIST 1.1 (PFS2)

Following discontinuation of study medication for PD by RECIST 1.1 as determined by investigator assessment, patients that started on subsequent therapy post-progression will continue to be followed at least every 12 weeks by investigator assessment for documentation of second progression. Subsequent therapy and OS will also be collected. Determination of PD for PFS2 will be by institutional call only. Patients who choose to continue on study therapy after the investigator confirmed PD will not be considered to have a second PFS-event until they have discontinued study medication and started subsequent anti-cancer therapy.

4.3.4 Overall survival follow-up

The OS period begins following determination of PFS2 by institutional call. In the OS follow-up period, all subsequent anti-cancer therapies will be documented by site personnel at least every 12 weeks until death, lost to follow-up, withdrawal of consent, or end of study, whichever comes first.

The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources, where it is possible to do so under applicable local laws. Sites have 5 days following the DCO for the final survival analyses to contact patients and provide complete survival data.

4.3.5 Patient management post-final analysis

Stopping criteria for the final analysis are defined in Section 9.3.

Patients receiving study drug, either savolitinib or sunitinib, will be allowed to remain on treatment for as long as they are deriving clinical benefit, in the opinion of investigator(s) or until meeting any discontinuation criteria defined in Section 3.8.

Patients will be monitored in accordance with the investigator's standard clinical practice and national product label (for patients being treated with sunitinib). Dispensing of study treatment post-final analysis will be done outside of IVRS/IWRS. At routine clinic visits, patients will return partially used and unused medication, and a thorough drug accountability assessment will be performed at the site.

AstraZeneca will collect information (during the treatment period and for 30 (±7) days after discontinuation of study medication) on SAEs, overdose and pregnancy (as per Section 6.3) via paper and emailed (preferably) or faxed directly to Tata Consultancy Services Data Entry Site (DES) (also known as AZ DES). Drug accountability information will be recorded in the source documents.

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca Patient Safety. Additionally, as stated in Section 6.3, any SAE or non-serious AE that is ongoing at the time of this data cut-off, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

5. STUDY ASSESSMENTS

The Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Tumour assessments by CT or MRI scans (RECIST 1.1)

The baseline assessment will be performed no more than 28 days prior to the date of randomisation and as close as possible to the start of study treatment. Following the baseline assessment, subsequent tumour assessments should be performed every 6 weeks at the start of each cycle (±7 days) during the first year and then every 12 weeks (±1 week) thereafter up to the time of BICR-confirmed PD. Anonymised copies of all CT/MRI scans done for tumour evaluation will be sent to an AstraZeneca appointed Contract Research Organisation (CRO) for blinded independent central review as soon as possible following completion of each scan (see Section 5.1.2). All scans should be evaluated using RECIST assessments until BICR-confirmed progressive disease.

At baseline, the imaging modalities used for RECIST assessment will be contrast-enhanced CT (MRI where CT is contraindicated) scans of the chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease. The same imaging modality should be use for subsequent follow-up assessments and will cover chest (in those patients with disease in the chest or upper abdomen lymphadenopathy at baseline), abdomen and pelvis with any other regions imaged at baseline where disease was present. Any other sites where new disease is suspected should also be appropriately imaged.

Radiological examinations performed in the conduct of this study should be retained at the site as source data.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit ±7-day window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than others.

5.1.2 Tumour evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment by determining progression free survival (PFS) times, objective response rates (ORR) and duration of response (DoR) and disease control rate (DCR). The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in Appendix F.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD or NE) will be calculated in comparison to the baseline tumour measurements obtained prior to randomisation.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

5.1.3 Central reading of scans/BICR

An independent review of all scans used in the assessment of tumours using RECIST 1.1 will be conducted. All imaging assessments including unscheduled scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO following completion of each scan. All scans will be read by BICR after notification of Progressive Disease by the investigator. If PD is not centrally confirmed, each subsequent scan will be read by BICR once it is received and processed by the CRO.

Every effort should be made by the institution to send each scan to the CRO as quickly as possible, so that Quality Control can be performed and the scans will be ready for review by the radiologists at the time that the patient develops Progressive Disease by institutional call. This scan, in particular, should be sent to the designated vendor without delay after acquisition, to minimise the turn-around time for confirmation of PD by BICR. Depending on

the speed and completeness of image submission to the sponsor-designated vendor, the turn- around time should generally be within 10 days.

During verification of the institution's diagnosis of radiographic progression by BICR, participants may continue to receive study treatment. The decision whether to continue or to withhold study treatment will be at the discretion of the investigator, but if not medically contra-indicated, patients should be encouraged to not start alternative anti-cancer therapy until confirmation of PD by BICR. If PD is not confirmed by BICR, the patient may continue/resume study treatment and must continue to undergo assessments as per Table 1, including scans at 6-week intervals (or sooner if felt to be medically indicated) until PD is confirmed by BICR. Those who begin subsequent non-study anti-cancer therapy prior to BICR-confirmed PD should continue to undergo tumour assessments, and sites must send each scan to the sponsor-designated vendor until PD is confirmed by BICR

After the primary PFS analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. The primary analysis of PFS for this study will be based on confirmation of PD using RECIST 1.1 by BICR.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1).

The following safety laboratory variables will be measured:

Table 2 Standard Laboratory Safety Assessment Panel

Clinical chemistry safety	**Haematology**
S/P-Albumin	B-Absolute leucocyte differential count
S/P-Alkaline phosphatase[2]	B-Eosinophils
S/P-ALT[2]	B-Haemoglobin
S/P-Amylase	B-Leucocyte cell count
S/P-AST[2]	B-Lymphocytes
S/P-Bilirubin, total[2,4]	B-Neutrophils
S/P-Calcium, total	B-Platelet count
S/P-Creatinine	**Urinalysis**
S/P-Free T4[3]	U-Dipstick-Blood
S/P-Glucose	U-Dipstick-Glucose
S/P-HbsAg[5], anti-HBc (qualitative), HBV DNA[6], HCV antibody, HCV RNA[7]	U-Dipstick-Ketones
S/P-Lactate dehydrogenase[3]	U-Dipstick- Leukocyte esterase or Leukocyte count
S/P-Magnesium	U-Dipstick-Protein[1]
S/P-Phosphate	
S/P-Potassium	
S/P-Sodium	
S/P-Thyroid Stimulating Hormone[3]	
S/P-Total Protein	
S/P-Urea nitrogen	

1 If 3+ or greater proteinuria is identified by dipstick assessment, a 24-hour urine collection for formal quantification of the level of protein excretion should be performed

2 Designates tests that are considered liver function tests (LFTs) and are to be done weekly x 9 and then at the start of every course thereafter. Guidelines for management of hepatotoxicity are in section 6.8.1.2 for savolitinib and section 6.8.2 for sunitinib

3 Thyroid function studies and LDH are to be done at the main study (Part 2) screening visit, and at the start of every cycle thereafter

4 If total bilirubin is >2x ULN, then fractionate into indirect and direct bilirubin

5 If the HBsAg test is negative, the anti-HBc test should be still performed

6 HBV DNA test should be available for all patients that have had a previous HBV infection or are positive for HBsAg

7 HCV RNA qualitative test is only needed if the HCV Ab test is positive, and must be negative for the patient to be eligible.

Unscheduled blood or urine samples may need to be taken at the onset and as a part of a follow-up of some SAEs. The results should be added to the clinical trial database.

In case a patient shows an AST or ALT ≥3 x ULN and total bilirubin ≥2 x ULN please refer to Appendix E 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

For blood volumes see Section 5.7.12

5.2.2 Physical examination

For timing of individual measurement refer to study schedule (see Table 1).

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems.

5.2.3 ECG, ECHO/MUGA

5.2.3.1 Resting 12-lead ECG

QTcF evaluation for the main study screening (Part 2) will be done based on triplicate 12 lead ECGs during the Part 2 screening period, every week in the first cycle, every cycle thereafter, and at the end of treatment as indicated in Table 1. Twelve-lead ECGs (triplicate) will be obtained after the patient has been rested in a supine position for at least 5 minutes. The investigator or designated physician will review the paper copies of the 12-lead ECGs. ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

5.2.3.2 ECHO or MUGA

An ECHO or MUGA scan to assess LVEF will be conducted during the main study (Part 2) screening period, every 12 weeks (±2 weeks) relative to the first dose of study medication, and at the end of treatment as indicated in Table 1. The modality of the cardiac function assessments must be consistent within a patient ie, if echocardiogram is used for the screening assessment then echocardiograms should also be done for subsequent testing. The patients should also be examined using the same machine and operator whenever possible.

5.2.4 Vital signs

Vital signs (heart rate, BP, temp) will be performed during the main study (Part 2) screening visit, during study treatment as per Table 1 and as clinically indicated.

Height will be assessed at the main study (Part 2) screening visit only. Weight will be assessed at the Part 2 screening visit, at the beginning of every cycle, and more frequently if clinically indicated. **The dose of savolitinib will not change for patients who started the study at <50 kg (ie, 400 mg), even if their weight increases to ≥50 kg during the course of the study.**

Any changes in vital signs should be recorded as an AE, if applicable.

5.2.4.1 Pulse and blood pressure

Blood pressure and heart rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size after 10 minutes rest on a bed. Blood pressure and pulse will be measured as per Table 1 and as clinically indicated thereafter.

The date of collection and measurement will be recorded on the appropriate eCRF.

5.2.4.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in Table 1.

The date of collection and measurement will be recorded on the appropriate eCRF.

5.2.5 Other safety assessments

5.2.5.1 Serum or urine pregnancy test

A pregnancy test on urine or blood sample will be performed for pre-menopausal women of childbearing potential, at the study screening visit, and prior to the first dose of study drug on Cycle 1 Day 1, at regular intervals during the study (monthly or at the time of a scheduled visit) and at treatment discontinuation. Tests will be performed by the institutional laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated and if positive, the patient will be discontinued from study treatment immediately.

5.3 Other assessments

5.3.1 Patient Reported Outcomes

Patient Reported Outcomes (PRO), an umbrella term referring to all outcomes and symptoms, as directly reported by the patient. Patient Reported Outcomes have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The sponsor obtained useful information about the effects of savolitinib in the phase II trial in PRCC, documenting

that patients appear to be stable in terms of their symptoms and their quality of life (as secondary endpoints) while on treatment. The same PRO tools (with the addition of a fatigue module to form the FACIT-F rather than just the FACT-G will be used in this phase III trial to evaluate the treatment effects on symptoms and HRQoL in relation to a clinical comparator (sunitinib). PRO questionnaires will be administered using PDAs (personal data assistant or a handheld PC).

All patients should complete the questionnaire Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19), Functional Assessment of Cancer Therapy – Fatigue (FACIT-F) and European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) at the scheduled clinic visit at Cycle 1 Day 1 pre-dose, and throughout the study at the times specified in the study plan (Table 1). The patient should continue to fill out the ePRO questionnaires until the EOT visit, at which time the last set will be completed by the patient. Health economic data will be collected until 30 days post-discontinuation of study medication (ie, the time of the Safety Visit). The e-PRO device should be returned at the EOT visit following the decision to discontinue study medication.

The site will train the patient on ePRO use during the first visit and have the patient fill out all four baseline questionnaires prior to any other activities, including being seen by the Investigator. It should take approximately 20 minutes to complete the questionnaires after the training. Thereafter, patients will be instructed to complete the PROs independently at home. It is important that the value and relevance of PRO data are explained carefully to participating patients so that they are motivated to comply with data collection. The research nurse or appointed individual should also stress that the information is confidential. If the patient has any medical problems he/she should discuss them with the doctor or research nurse separately from their PRO assessment. The site should check to ensure that the PRO data has been entered (ie, patient compliance) on the web-based portal during every site visit. **Similarly, at the EOT visit, the patient should fill out all four questionnaires prior to being seen by the Investigator.**

The instructions for completion of questionnaires are as follows:

- The patient must complete the questionnaires themselves without any intervention from family, friends, centre staff etc.
- The only exception to this is if the patient is blind or illiterate. In this case the questionnaires may be read to the patient verbatim, however the reader must not aid in the interpretation of questions or in the selection of answers.
- Only one answer to every question should be checked.

- Should the patient come to the centre for a visit without having completed the assessments independently at home, they should do so while at the site visit. In such cases:
  - The assessments must be completed before any investigations or discussions about the patient's disease with the clinic staff.
  - Centre personnel should not review the responses to the questions with the patient or with any other centre staff.

5.3.1.1 Functional Assessment of Chronic Illness Therapy – Fatigue

The validated Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (now in Version 4) is a 40-item instrument. It comprises the 4 domains from the FACT-G (Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being) as well as a 13-item 'additional concerns' domain that captures information about fatigue. (Appendix I).

5.3.1.2 Functional Assessment of Cancer Therapy Kidney Symptom Index-19

The Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19) is a validated instrument designed to accurately assess patient self-reported symptom burden to determine treatment impact and evaluate clinical benefit in patients with renal cancer (Rao et al 2009). The instrument includes 19 items covering 4 subscales: Disease-Related Symptoms Subscale – Physical, Disease-Related Symptoms Subscale – Emotional, Treatment Side Effects Subscale, Function and Well-Being Subscale; responses are reported as it applies to the past 7 days (Appendix J).

5.3.1.3 European Quality of Life-5 Dimensions-5 Levels

The EQ-5D is a standardised measure of health status developed by the European Quality of Life (EuroQoL) Group in order to provide a simple, generic measure of health for economic appraisal (EuroQoL Group 2015), see Appendix J. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the economic evaluation of health care. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQoL Group 2015). The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale (VAS), where the patient will be asked to rate their current health status on a scale of 0 to 100, with zero being the worst imaginable health state.

5.3.1.4 PRO CTCAE

The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system has been developed by the National Cancer Institute (NCI).

The PRO-CTCAE will only be administered in the US, Italy, France, and South Korea where a linguistically-validated version exists. PRO-CTCAE is an item-bank of symptoms experienced by patients while undergoing treatment of their cancer. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Sprangers et al 1992; Litwin et al 1999; Basch et al 2009). To date, 81 symptoms of the CTCAE have been identified to be amenable to patient reporting. These symptoms have been converted to patient terms (eg, CTCAE term "myalgia" converted to "aching muscles"). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. For other symptoms like rash, additional questions focus on the presence on the body. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. These items and the additional questions for some of the symptoms have been extensively evaluated by cancer patients, using cognitive testing methods, to be clear, comprehendible, and measure the symptom of interest. Not all items are administered in any one clinical trial. The questionnaire in Appendix J contains only those items which are considered relevant for the trial, site of cancer, and cancer treatment.

5.3.2 Hospital resource use

Site staff should review hospital notes for any hospital visits and procedures that were not part of the study visits and complete the AZ Hospital Admissions (HOSPAD) oncology module as required starting Cycle 1 Day1 of the study and for 30 days post-drug discontinuation until the Safety Follow-up visit.

HOSPAD is a short form that the site staff should complete whenever the patient attends any inpatient or outpatient hospital visit that is not part of the study protocol, including admissions, ER visits etc. The form asks for information on the type of visit (ER, clinic, hospital stay, and ICU) and length of stay where relevant. In addition, it contains a list of presenting symptoms /signs that the patient has upon arrival. If the patient requires a hospitalisation, HOSPAD automatically reminds the study staff to complete the SAE modules.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Venous blood samples (2 mL) will be collected from patients receiving savolitinib at the times detailed in Table 1 and Table 3 for determination of plasma concentrations of savolitinib, and of M2 and M3, the major metabolites of savolitinib. The date/time of the last two doses given prior to the PK sample, as confirmed in the patient diary, as well as the date/time the PK sample is drawn and the dose/time that savolitinib is given on the PK day need to be recorded

in the eCRF. Plasma concentrations will be analysed by Covance on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

In addition, a 2-mL blood sample for PK analysis should be drawn as soon as feasible after the patient is diagnosed with abnormal LFTs necessitating drug interruption. The date and time of the last savolitinib dose must be recorded in the eCRF.

Table 3 Pharmacokinetic savolitinib blood sampling schedule

Day	Time for blood sample collection (2 mL)
Cycle 1 Day 1	Single Sample: Pre-dose
Cycle 1 Day 15	Pre-Dose, and 1 and 3 hours post-dosing
Cycle 1, Day 29	Single Sample: Pre-dose
Cycle 2, Day 15 (day 57)	Single Sample: Pre-dose
At the time that the patient is diagnosed with abnormal LFTs necessitating drug interruption.	ASAP after abnormal LFTs necessitating drug interruption.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.4.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by the sponsor-designated laboratory, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the reproducibility evaluation will not be reported in the Clinical Study Report, but separately in a Bioanalytical Report.

Any residual back-up PK samples may be used for future [redacted] (in this case, residual back-up PK samples will be shipped to AstraZeneca Biobank, see details in the Laboratory Manual).

5.5 Pharmacodynamics

5.5.1 Collection of samples

Pharmacodynamic samples from blood will not be collected during the study. However, on treatment tumour samples from patients who have had a response or stabilisation on either drug can be collected at the time of relapse [redacted]

5.6 Pharmacogenetics (Appendix C)

The subject's consent to participate in the genetic research components of the study is optional. The background, rationale, objectives, and inclusion/exclusion criteria for the genetic analysis are detailed in Appendix C: Genetics Research. Please refer to Appendix C and the Laboratory manual for further information surrounding the timing of blood sample collection, storage, and destruction.

5.7 Biomarker analysis

Biological samples (eg, tumour or blood) will be collected as detailed in the Laboratory Manual for the reasons listed below:

[redacted]

5.7.1 NGS analysis to determine MET-driven status of tumour biopsy sample

See section 5.7.2 for information on appropriate specimens for Part 1 screening. The Laboratory Manual provides the required tissue specifications.

The tumour sample will be used to test for the following molecular alterations:

- Chromosome 7 gain
- *MET* amplification
- *MET* kinase domain mutations
- *HGF* amplification
- *FH* mutation
- *VHL* mutation

Genomic alterations in chromosome 7, *MET* or *HGF* genes will be used to determine MET-status and potential eligibility for the main study.

Genomic alterations in *FH* and *VHL* genes will be used to exclude patients, as described in Section 1.2.5.

5.7.2 Collection, analysis and reporting of tumour samples

Following the Part 1 screening visit and signing of the ICF, an FFPE tumour sample meeting the requirements specified in the Laboratory Manual will be sent to the sponsor-designated central laboratory. For first-line patients, the diagnostic specimen should be used. For previously treated patients, the most recent archival specimen obtained during a clinical procedure is preferable to the diagnostic specimen only if it meets specifications and has an equal or higher tumour cellularity. Fine needle aspirate FFPE cell blocks will not provide sufficient tumour and as such are not allowed.

If the above is not available or unlikely to yield sufficient material for testing, the patient will have the option to provide an FFPE tumour tissue block from a de-novo core needle tumour biopsy. The biopsied tumour should preferably not be a RECIST target lesion. Consideration should be given to the potential benefit to the patient (should they be eligible for the main study) in the context of the risk posed by the biopsy procedure. Tissue biopsy sampling should be conducted in appropriate clinical settings in accordance with expert guidelines, only by investigators experienced in performing these sampling methods.

Please refer to the Laboratory Manual for further details regarding sample selection, retesting procedures etc.

For each sample that passes tissue sample quality control, the sponsor-designated central laboratory will generate a clinical trial assay (CTA) report detailing the presence or absence of qualifying genomic alterations for MET-driven status.

5.7.3 Exploratory use of data generated from the sponsor-designated central laboratory testing of tumour samples

The designated, investigational SAVOIR clinical trial NGS assay involves the analysis of 2 genes and chromosome 7 data for the presence of qualifying alterations (ie, MET-driven) and of 2 genes for the presence of alterations governing exclusion in this study. The underlying gene panel used in this investigational test is based on the sponsor designated central laboratory's clinical-grade cancer gene profiling test which analyses the coding sequence of 310 cancer-related genes plus select introns from 31 genes for variants and/or rearrangements. A full list of all genes is available in the Laboratory Manual.

[redacted]

The results of the biomarker analysis of the other cancer-related genes can be requested by the investigator under the conditions outlined in the Genomic Testing Manual.

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

5.7.7 Collection of tumour samples for exploratory analysis at disease progression (optional)

All patients will be asked to provide consent (in the Main ICF or at EOT) for a biopsy for fresh tumour tissue at disease progression (see Laboratory Manual for specifics). This biopsy is strongly encouraged, but optional. Such collections are particularly encouraged for patients who derived benefit from study medication and subsequently relapse or discontinue drug. This sample will be used to help understand the mechanisms of relapse to either study medication.

5.7.8 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study medication to generate hypotheses to be tested in future research.

5.7.9 Labelling and shipment of biological samples (Appendix B)

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria) see Appendix B'IATA 6.2 Guidance Document'. Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.7.10 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from all patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca Biobank during the entire life cycle.

5.7.11 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures that AstraZeneca is notified immediately of the patients' withdrawal of informed consent for the use of donated samples.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

5.7.12 Volume of blood

The volume of blood that will be drawn from each patient during the study will vary depending upon the length of participation, patient consent to [redacted] and standard practices.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of established methods. The number of samples/volumes is therefore subject to centre-specific changes. Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or additional PK assessment.

The total volume of blood drawn from each patient receiving a minimum of 24 weeks of treatment in this study is as follows:

Table 7 Volume of blood to be drawn from each patient in the first 24 weeks

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistries and LFTs (including thyroid hormones, LDH)	8 mL	5	40
	Clinical chemistry and LFTs	4 mL	4	16
	LFTs	4 mL	4	16
	Hepatic screening	8 mL	1	8
	Haematology	4 mL	9	36
	Coagulation	5 mL	1	5
Pharmacokinetics		2 mL	6	12
[redacted]		10 mL	3	30
[redacted]		10 mL	6	60
[redacted]		20 mL	1	20
Pharmacogenetics (optional)		10 mL	1	10
Total			41	253

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

Liver enzyme and bilirubin abnormalities, as well as any clinical adverse events associated with liver dysfunction will be reported on a quarterly basis to the FDA.

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

6.1.1 AEs of special interest – hepatic disorders

A thorough review of the patients who developed significant hepatotoxicity on savolitinib was undertaken. As of 30 August 2016, 387 patients/healthy volunteers have received at least 1 dose of savolitinib. Of these, 108/325 (33%) reported 303 AEs in the Hepatic Disorders SMQ. Per-patient multiple hepatic event reporting, either simultaneously or sequentially, was frequent. The most common hepatic AE was an increase in liver enzyme values (ALT, AST, ALP, or bilirubin) accounting for 221/303 events (73%), of which 22/303 (7.2%) events were serious. Overall, most liver enzyme AEs were considered by the investigator to be related to study medication (171/221 events, 77%). Most were mild or moderate in severity (171/221 events, 77%), and resolved without reduction or interruption of savolitinib (164/221 events, 74%). Fifteen of 22 serious hepatic events were considered causally related to savolitinib and 4/22 not related.

The onset of hepatic toxicity was within 1 week of exposure for 52/221, 23% of events. Over the subsequent 3 weeks, a further 110/221, 50%, events began; however, later events can develop. Ninety-five percent of events occur within the first 10 weeks. Time to resolution was up to one week in 30/303, 10%; 85/303, 28%, took between 1 and 2 weeks to resolve and 55/303, 18%, took 2 to 4 weeks to resolve. Ten patients had combined bilirubin and ALT/AST elevations consistent with potential Hy's law. Three of these patients had no other explanation for the liver biochemistry abnormalities other than liver injury caused by the savolitinib and therefore met the criteria for Hy's law. One of these 3 patients experienced a fatal event of hepatic encephalopathy and the investigator felt that there was a reasonable possibility that the event may have been caused by the savolitinib.

The hepatic adverse effect profile of savolitinib is similar to other tyrosine kinase inhibitors (TKIs), ie, a high frequency of low grade enzyme elevations and much less frequent higher-grade enzyme elevations. In general, with savolitinib, these events resolve within 2 months without dose changes. Possible confounders, the majority of which were concomitant medications with labelled hepatic adverse reactions, were of numerically limited influence, ie, reported in no more than 25% of adverse events. The hepatic event profile of savolitinib is likely to be a true drug effect, given its frequency and its consistency with other TKIs. The severity is generally low, the events are self-limiting, while being slow to resolve. Dose changes or drug discontinuation occurred in 25% of the events. On savolitinib, a rise in hepatic enzymes or bilirubin requires close monitoring until resolution, and if persistent or increasing in severity, the study medication should be interrupted or discontinued. Some patients can be successfully re-challenged at a lower dose and those with lower-grade elevations may be able to continue the drug with subsequent improvement.

Pharmacokinetic/pharmacodynamic modelling of hepatotoxicity data as of 30 June 2016 showed a link between exposure (AUC and C_{min}) and high-grade liver elevations. Preliminary univariate extreme value modelling showed a weak-to-moderate level of evidence of a relationship between BW (body weight) and maximum LFT elevation. Patients with lower body weights may therefore be at greater risk of hepatotoxicity. A BW cut-off of 50 kg is predicted to 1) provide maximum exposures in line with the upper 90% percentile of heavier individuals, perhaps reducing hepatotoxicity risk and 2) provide minimum exposures above the minimum predicted exposure associated with the 600 mg QD dosing. Higher cut-offs may result in exposures significantly below the observed 600 mg QD exposure range. Therefore, a 400-mg dose for patients below 50 kg will be used to potentially reduce the risk of hepatotoxicity.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

In the Part 1 screening period, only SAEs related to study procedures must be reported (AEs do not require reporting). From the signature of the main (Part 2) ICF onwards, throughout the treatment period and up to and including the 30-day follow-up period all AEs/SAEs must be reported.

6.3.2 Follow-up of unresolved adverse events

Any AE/ SAE/ abnormal laboratory findings that are ongoing at the time of study treatment discontinuation or any new treatment related events within 30 days of last study treatment, must be followed up to resolution or until the event becomes stable (or returns to baseline) or is unlikely to resolve further in the opinion of the investigator. AstraZeneca retains the right

to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim).
- The date and time when the AE started and stopped.
- Worst CTCAE grade and changes in grade during the course of the AE.
- Whether the AE is serious or not.
- Investigator causality rating against the Investigational Product (IP) (yes or no).
- Action taken with regard to IP.
- AE resulted in patient's withdrawal from study (yes or no).
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE.
- Date Investigator became aware of serious AE.
- AE is serious due to (provide all seriousness criteria applicable).
- Date of hospitalisation (if applicable).
- Date of discharge (if applicable).
- Probable cause of death (if applicable).
- Date of death (if applicable).
- Autopsy performed (if applicable).
- Causality assessment in relation to Study procedure(s).
- Causality assessment to other medication.
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

The grading scales found in the National Cancer Institute (NCI) CTCAE will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades

the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation program website (http://ctep.cancer.gov).

6.3.4 Causality collection

The investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient during the visit or in the eDiary or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs or cardiac evaluations should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3xULN together with total bilirubin ≥2xULN may need to be reported as SAEs. Please refer to Section 6.8.1.2 and Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study (DUS) and/or increases in the symptoms of the cancer. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site staff inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the Web Based Data Capture (WBDC system), an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference safety document for the definition of expectedness/listedness is Section 5.4 of the Investigator's Brochure for savolitinib and the EU Summary of Product Characteristics (SPC) for the active comparator, sunitinib.

6.5 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of investigational product that is considered both excessive and medically important. For further dosing information please refer to the IB.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study medication occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies occurring during the study in patients taking savolitinib, and their outcomes, should be reported to AstraZeneca except when the pregnancy is discovered before the study subject has received any study medication. Pregnancies and their outcomes in female partners of patients occurring up to 6 months after the male patient has discontinued savolitinib should be reported to AstraZeneca. Pregnancies occurring during the study in patients on sunitinib should be reported both to AstraZeneca and to Pfizer.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study medication should be discontinued immediately.

For patients taking savolitinib, pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs for patients taking savolitinib. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study. If pregnancy occurs in patients taking sunitinib during the course of the study, adverse outcomes as listed above, should be reported as SAEs to AstraZeneca and Pfizer.

If any pregnancy occurs in patients during the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Because studies in animals taking savolitinib have shown abnormalities in sperm development, male patients taking savolitinib should refrain from fathering a child or donating sperm during the study and for 6 months following their last dose.

Pregnancy in the partner of a patient is not considered to be an AE. However, the outcome of all pregnancies in partners of patients taking savolitinib (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented in the Pregnancy Outcome Reporting Form. Consent from the pregnant partner must be obtained (Pregnant Partner ICF) before the Pregnancy Outcome Reporting Form is completed.

6.7 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study medication that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred.
- was identified and intercepted before the subject received the drug.
- did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported as medication errors:

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong patient received the medication (excluding IVRS/IWRS errors).
- Wrong drug administered to patient (excluding IVRS/IWRS errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error.
- Subject accidentally missed drug dose(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Patient failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product.

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of study medication-related toxicities - dose reductions and modifications

Toxicity will be assessed utilizing the NCI CTCAE (https://evs.nci.nih.gov/ftp1/CTCAE/), unless otherwise specified.

Table 8 outlines the Dose Level Reductions for each study medication. A maximum of two dose reductions will be allowed for both drugs, unless the patient has started at a savolitinib dose of 400 mg due to weight <50 kg, where only one dose reduction is allowed. No dose re-escalations are allowed. Immediate management of situations not covered by the guidelines below should be as medically indicated and with temporary suspension of study medication as appropriate, with follow up management carried out in consultation with the AstraZeneca study physician.

Table 8 Dose level reductions of study medications

Dose level	Savolitinib PO daily dose	Sunitinib PO daily dose 4 weeks on/2 weeks off
Starting dose	600 mg QD	50 mg
-1 Dose level	400 mg QD	37.5 mg
-2 Dose level	200 mg QD	25 mg

PO, Oral; QD, Once daily

6.8.1 Management of savolitinib-related toxicities

Dose modification guidelines for savolitinib study drug-related toxicities are provided in the following sections. Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. Prior to discontinuation of study drug due to toxicities please consult with the AstraZeneca study physician. Please see Section 6.8.1.1 for management of savolitinib-specific toxicities including dermatologic toxicity, pyrexia and hypersensitivity, Section 6.8.1.2 for hepatotoxicity management guidelines, Section 6.8.1.3 for dose modifications due to other savolitinib-related toxicity, Section 6.8.1.4 for dose modifications for savolitinib-related QTcF prolongation, and Section 6.8.1.5 for risk minimisation activities for identified and potential risks associated with savolitinib.

6.8.1.1 Guidance for management of savolitinib specific toxicities

[redacted]

6.8.1.2 Dose modification due to savolitinib-related hepatotoxicity

- Promptly evaluate patients with elevated LFTs during study treatment for alternative aetiologies and potential Hy's law criteria (ALT or AST ≥3x ULN **together with** TBL ≥2xULN) and discontinue potential contributing concomitant medications or alternative causal agents, as well as anti-coagulants, if appropriate.

- Ensure a PK sample is collected as soon as feasible after the patient is diagnosed with abnormal LFTs necessitating drug interruption. The date and time that the PK sample was drawn and the date and time of the last savolitinib dose prior to the PK sample must be recorded in the eCRF.

If a patient discontinues due to an LFT abnormality, LFT monitoring should continue until resolution to grade 1 or baseline or an apparent plateau has been reached.

1 Discontinue savolitinib if
   - ALT or AST >8x ULN, or
   - ALT or AST >5x ULN for >2 weeks, or
   - ALT or AST >3x ULN and (TBL>2x ULN or INR>1.5 if not on anticoagulants that elevate the INR).
   - AST or ALT >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5%
2 Withhold savolitinib if ALT or AST >5-8x ULN without TBL elevation above baseline or ULN, repeat LFT testing twice a week for 1 week;
   - If improved to grade 1 or baseline in 1 week, resume at reduced dose with LFT testing twice a week for 6 weeks;
   - If not, discontinue
3 Withhold savolitinib if ALT or AST >3x ULN and concurrent TBL 1.5~2x ULN, repeat LFT testing twice a week for 1 week,
   - If both ALT/AST and TBL improve to grade 1 or baseline in 1 week, resume at reduced dose with LFT testing twice a week for 6 weeks
   - If not, discontinue
4 Continue savolitinib if ALT or AST >3-5x ULN without TBL elevation above baseline or ULN, repeat LFT testing every week
   - If ALT or AST are trending upward, withhold dosing and repeat LFT twice a week for 1 week;
   - if improved to grade 1 or baseline in 1 week, resume at same dose with LFT testing every week for 6 weeks
   - if improved to grade 1 or baseline in 2 weeks, resume at reduced dose with LFT testing every week for 6 weeks
   - If not, discontinue
5 Discontinue savolitinib for recurrent Grade 3 ALT or AST (>5x ULN)
6 Discontinue savolitinib for recurrent Grade 2 ALT or AST (>3-5x ULN) and TBL >1.5~2x ULN
7 Withhold savolitinib for recurrent Grade 2 ALT or AST >3-5x ULN without TBL elevation above baseline or ULN, repeat LFT testing twice a week for 1 week
   - if improved to grade 1 or baseline in 1 week, resume at reduced dose with LFT testing every week for 6 weeks;

– if not, discontinue savolitinib.

6.8.1.3 Dose modifications due to other savolitinib-related toxicity

Table 9 Dose modifications for savolitinib-related toxicities

NCI CTCAE toxicity grade	Action
Grade 0, 1, or 2	None
Grade 3[a]	Hold savolitinib and follow the algorithm below:
• Grade 3 toxicity for ≤7 days and resolves to ≤Grade 2 or baseline within 14 days of onset • Toxicity persists at Grade 3 for >7 days	• Resume dosing at same dose or one reduced dose level (maximum of 2 dose reductions) as clinically appropriate • Discontinue savolitinib
Grade 4	Follow the algorithm below:
• Expected to be manageable/reversible with dose reduction • Not expected to be manageable/reversible with dose reduction	• Hold dosing and consult with AstraZeneca study physician • Discontinue savolitinib
Recurrence of Grade 3	
• Grade 3 toxicity for ≤7 days and resolves to ≤Grade 2 or baseline within 14 days of onset • Grade 3 toxicity for >7 days	• Resume dosing at same dose or one reduced dose level (maximum of 2 dose reductions) as clinically appropriate • Discontinue savolitinib
Recurrence of Grade 4	• Discontinue savolitinib

No more than 2 dose reductions will be allowed for any patient. Patients on 400 mg savolitinib due to weight <50 kg will only be allowed one dose reduction. Patients requiring additional dose modifications due to toxicity will discontinue study treatment.

[a] Despite appropriate supportive care

6.8.1.4 Dose modifications for savolitinib-related QTcF prolongation

Dose modifications for savolitinib-related QTcF prolongation are reported in Table 10

Table 10 Dose modifications for savolitinib-related QTcF prolongation

NCI CTCAE toxicity grade	Action
Grade 0, 1, or 2	None
Grade 3	Hold dosing and follow algorithm below
• Patients with QTcF prolongation to >500 msec on at least two separate ECGs • If the toxicity does not resolve to QTcF <481msec within 21 days	• Consult with a cardiologist to validate ECG finding. Ensure cardiac surveillance and take actions in accordance with clinical standard. Regular ECGs performed until resolution to QTcF <481 msec and then restart drug at one reduced dose level • Discontinue study drug and consult with a cardiologist for further management as clinically indicated
Grade 4	
• QTcF ≥501 or >60 msec change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	• Discontinue study drug and consult with a cardiologist for further management as clinically indicated

6.8.1.5 Risk minimisation activities for identified and potential risks associated with savolitinib

The following section highlights risk minimisation activities for the key identified and potential risks identified in either preclinical studies or from ongoing clinical studies.

Identified risks

Liver Function Tests

Drug-induced liver injury (DILI) is an AESI for savolitinib and requires specific monitoring. For more information see Section 6.1.1 or the most current version of the IB. Weekly monitoring of liver function tests will be done for the first 9 weeks and then at the start of every cycle thereafter. The hepatotoxicity management algorithm (Section 6.8.1.2) now clearly defines and limits the patients on savolitinib who can be re-challenged to those with lower grade abnormalities with rapid resolution. As stated in the eligibility criteria and risk mitigation sections, patients with significantly abnormal baseline liver function tests will be excluded from the study. In addition, as mentioned in Section 6.1.1, a 400-mg dose for patients below 50 kg will be used to potentially reduce the risk of hepatotoxicity.

Pyrexia and hypersensitivity

Pyrexia and hypersensitivity have been identified as a risk for patients receiving savolitinib. Pyrexia was followed in some cases by DILI (see above) or an association of symptoms

suggestive of hypersensitivity such as, but not limited to, allergic rash, cytopenias, myalgia/arthralgia [redacted] Patients who experience pyrexia with or without an association of the above symptoms after initiation of savolitinib treatment must follow the toxicity management guidelines.

QTc prolongation

QTc interval prolongation potential of savolitinib 600mg was assessed in a thorough QT study in healthy volunteers. Analysis of the data concluded that it is a positive study as the upper two-sided 90% CI for the mean ΔΔQTcF was 13.6 and 14.0 msec at 4 and 5 hours, respectively. Regular ECG assessments will be done throughout the study according to the study plan. Patients who present ECG abnormalities with or without symptoms during treatment with savolitinib must follow the QTc prolongation toxicity management guidelines.

Oedema

Peripheral oedema has been observed in patients receiving savolitinib. These events have been Grade 1 or 2, and the incidence does not appear to be dose related. Oedema has also been observed with other MET inhibitors including onartuzumab and crizotinib. Oedema should be monitored by clinical examination and measurement of weight. Diuretic therapy should be considered at the discretion of the investigator. Renal function will be carefully monitored.

Nausea/vomiting

Nausea and/or vomiting are common causally related AEs seen in clinical trials of savolitinib. If vomiting occurs after taking savolitinib, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of savolitinib. Patient reports of nausea and vomiting are expected to be evaluated and treated by investigators according to local practice (eg, use of antiemetic therapy, intravenous fluid replacement).

Fatigue

Fatigue is one of the more common causally related AEs seen in clinical trials of savolitinib. Follow the general guidance in the protocol for dose interruptions/reductions/ discontinuations as per Section 6.8.1.

Potential risks

Phototoxicity and/or rash

Results of an in vitro (3T3) test suggest the potential for phototoxicity. Measures to prevent photosensitivity have been included in ongoing studies. There have been no reported cases of photosensitive rash. Adverse events of Grade 1 rash, erythema and pruritus have been reported in some patients. During savolitinib therapy and for 4 weeks after the last dose, patients should be advised to avoid prolonged exposure to sun, wear protective clothing and a

hat and seek shade from the sun as far as possible; in addition, an SPF30+ sunscreen should be used. Exposure to other sources of UV light including sunbeds, tanning booths, etc. should be avoided. If sunburn occurs, it is important to discontinue the study medication and take action under the direction of a doctor. Keeping the area of skin eruption moist and applying wet dressings may help relieve the symptoms. Reactions may last a few days, however severe reactions may last up to a few weeks. Topical steroid creams may be helpful in treating the redness, and antihistamines are generally helpful in minimizing the itching. In severe cases, a short course (10-14 days) of oral steroids, under the direction of a doctor, can be used.

Testicular toxicity

In the 3-month GLP dog study, histopathological findings were seen in the testes (seminiferous tubular degeneration) and/or epididymides (cellular debris, reduced cellularity/sperm) at all doses levels. Group mean exposures in male dogs at the lowest observed effect level (LOEL) were approximately 4-fold above the group mean AUC in patients at the 600 mg QD dose (17.06 µg/mL). A no observed effect level (NOEL) was not identified for the testicular/epididymal findings. Reversibility was not assessed in this study, but lesions of this nature and severity (minimal to mild) would be expected to recover given sufficient time off-dose.

Male patients taking savolitinib must use a condom during sexual intercourse with a female partner of childbearing potential (pregnant or not) and refrain from donating sperm during the study and for 6 months after their last dose.

6.8.2 Management of sunitinib-related toxicities

Table 11 Dose modifications for sunitinib-related toxicities (including hepatic)

NCI CTCAE toxicity grade	Action
Grade 0, 1, or 2	None
Grade 3[a]	Hold sunitinib and follow the algorithm below:
• Toxicity at Grade 3 for ≤7 days and resolves to ≤Grade 1 or baseline • Toxicity persists at Grade 3 for >7 days	• Resume dosing at one reduced dose level (maximum of 2 dose reductions) • Discontinue sunitinib
Grade 4	Follow the algorithm below:
• Expected to be manageable/reversible with dose reduction • Not expected to be manageable/reversible with dose reduction	• Hold dosing and consult with AstraZeneca study physician • Discontinue sunitinib
Recurrence of Grade 3	
• Grade 3 toxicity for ≤7 days and resolves to ≤Grade 1 or baseline • Grade 3 toxicity for >7 days	• Resume dosing at one reduced dose level (maximum of 2 dose reductions) • Discontinue sunitinib
Recurrence of Grade 4	• Discontinue sunitinib

No more than 2 dose reductions will be allowed for any patient. Patients on 400 mg savolitinib due to weight <50 kg will only be allowed one dose reduction. Patients requiring additional dose modifications due to toxicity will discontinue study treatment.

[a] Despite appropriate supportive care

6.8.2.1 Risk minimisation activities for risks associated with sunitinib

Adrenal function: Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Dermatologic: Severe cutaneous reactions have been reported with sunitinib, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of SJS, TEN, or EM (eg, progressive skin rash often with blisters or mucosal lesions) are present, sunitinib should be discontinued. If a diagnosis of SJS or TEN is suspected, sunitinib must not be re-started.

Hepatic: Sunitinib has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Sunitinib should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart sunitinib if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Hypertension: Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. Interruption and re-initiation at a reduced dose should be implemented as per Table 8. Grade 3 hypertension (>160/100, more intensive therapy than was previously used indicated) was observed in 50/375 treatment-naïve RCC patients (13%) on sunitinib. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 32/375 treatment-naïve RCC patients (9%) on sunitinib.

Hypoglycaemia: Sunitinib has been associated with symptomatic hypoglycemia, which may result in loss of consciousness, or require hospitalisation. Hypoglycemia has occurred in clinical trials in 2% of the patients treated with sunitinib for RCC. Reductions in blood glucose levels may be worse in diabetic patients. Check blood glucose levels regularly during and after discontinuation of treatment with sunitinib. Assess if anti-diabetic drug dosage needs to be adjusted to minimise the risk of hypoglycemia.

Infections: Necrotizing fasciitis, including fatal cases, has been reported in patients treated with sunitinib, including of the perineum and secondary to fistula formation. Discontinue sunitinib in patients who develop necrotizing fasciitis.

Myocardial dysfunction/CHF: Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Blood pressure should be monitored and managed promptly. In the presence of clinical manifestations of congestive heart failure (CHF), sunitinib should be discontinued. The dose should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Pancreatitis: Pancreatitis was observed in 5 (1%) patients receiving sunitinib for treatment-naïve RCC compared to 1 (<1%) patient receiving IFN-α. If symptoms of pancreatitis are present, patients should discontinue sunitinib.

Proteinuria: Interrupt treatment for 24-hour urine protein ≥3 grams and dose reduce. Discontinue for nephrotic syndrome or repeat episodes of protein ≥3 grams/24 hours despite dose reductions.

Thyroid Dysfunction: Patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, on sunitinib treatment. All patients should have monitoring of thyroid function performed as per Table 1 and be treated as per standard medical practice.

Tumour Lysis Syndrome (TLS): Cases of TLS, some fatal, have been observed in patients treated with sunitinib. Patients generally at risk of TLS are those with high tumour burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

Thrombotic Microangiopathy (TMA): Thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients treated with sunitinib. Discontinue sunitinib in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

Wound healing: Cases of impaired wound healing have been reported during sunitinib therapy. Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of study medications

AstraZeneca will supply savolitinib tablets for oral use. The tablets will be supplied in the 200-mg strength, in open-labelled high-density polyethylene (HDPE) bottles. Additional information about the investigational product may be found in the IB.

Sunitinib will be sourced locally in US and dispensed by the sites. In other countries, Sunitinib will be packed, labelled and distributed by AZ through the IVRS/IWRS.

Sunitinib will be the commercial carton supplied by Pfizer. The original carton will be the labelled with a clinical study label and contain the original blister packs and English language patient information leaflet.

Table 12 IP strength and manufacturer

Investigational product	Dosage form and strength	Manufacturer
Savolitinib	200 mg tablets	AstraZeneca, Sweden
Sunitinib	25 mg & 12.5 mg capsules	Pfizer

7.2 Dose and treatment regimens

7.2.1 Savolitinib

Savolitinib will be dosed as follows:

For patients ≥50 kg at the start of treatment, savolitinib 600 mg PO QD, and for patients <50 kg at the start of treatment, savolitinib 400 mg PO QD will be administered in 42-day (6-week) treatment cycles.

Savolitinib is to be administered with a meal. The time of day for administration of savolitinib should be consistent and the actual time the dose is taken should be recorded in the eDiary each day.

On scheduled PK collection days and clinic visit days the patient should be instructed to wait until he/she arrives at the study centre to take their study medication with a meal when instructed.

If the patient misses a dose of study medication, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due.

If vomiting occurs after taking the study medication, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of savolitinib. If vomiting persists, the patient should contact the investigator. Ondansetron or another serotonin-receptor antagonist may be used.

Patients should be instructed to bring any unused savolitinib in the original bottles, in addition to returning any empty bottles to each clinic visit. Savolitinib dosing compliance/drug diary should be reviewed with the patient at each clinic visit, including the visit at the beginning of each cycle when study medication is dispensed.

7.2.2 Sunitinib

Sunitinib: two 25 mg capsules PO QD, with or without food will be administered in 6-week treatment cycles: 4 weeks on/2 weeks off.

The time of day for administration of sunitinib should be consistent and the actual time the dose is taken should be recorded in the eDiary each day.

If the patient misses a dose of study medication, it should be taken as soon as it is remembered. A missed dose should not be taken, though, if it is close to the next dose. In this case, the next dose should be taken at the regular time. More than 1 dose of sunitinib should not be taken at a time.

If vomiting occurs after taking sunitinib, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of sunitinib. If vomiting persists, the patient should contact the investigator. Ondansetron or another serotonin-receptor antagonist may be used.

On clinic visit days the patient should be instructed to wait until he/she arrives at the study centre to take their study medication when instructed.

Patients should be advised to bring any unused sunitinib in the original blister packs, in addition to returning any empty blister packs to each clinic visit. Sunitinib dosing compliance

should be reviewed with the patient at each clinic visit, including the visit at the beginning of each cycle when study medication is dispensed.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling, where applicable for that country. Label text will be translated into local language.

7.4 Storage

All study medications should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack specifies the appropriate storage.

7.5 Compliance

The administration of study medications should be recorded in the appropriate sections of the eCRF. Treatment compliance will be assessed by the tablet or capsule count and the information should be recorded in the appropriate section of the eCRF.

An eDiary will be provided to all patients. Patients will be asked to record the date and time of their self-administered doses in the eDiary on all study days in order to monitor compliance and aid in PK data interpretation for those taking savolitinib.

7.6 Accountability

The study medications provided for this study will be used only as directed in the Clinical Study Protocol. Details of treatment with investigational product for each patient will be recorded in the eCRF.

Patients must return all unused medication and medication containers to the clinic at the time of every visit for a pill count and reconciliation with the eDiary.

The study site staff at the investigational site will account for all drugs dispensed and returned and for appropriate destruction. Certificates of delivery, destruction and return must be signed.

7.7 Concomitant and other treatments

7.7.1 Permitted concomitant medications and treatments

Blood transfusions are allowed during the study.

Patients are permitted to receive granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) in accordance with the American Society of Clinical Oncology's (ASCO) guidelines

Patients may receive bisphosphonates and/or RANK ligand inhibitors like denosumab, or corticosteroids for the treatment of bone metastases. However, patients receiving sunitinib should avoid invasive dental procedures if they have ever received bisphosphonates. Any patient who has received bisphosphonates requires a maxillofacial exam prior to randomisation (see Table 1).

Limited field palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period.

7.7.2 Restrictions based on clinical pharmacology for both study medications

Refer to Appendix H for concomitant medications that should be restricted or used with caution.

Patients who have taken strong inducers or inhibitors of CYP3A4 or strong inhibitors of CYP1A2 within 2 weeks of randomisation are excluded from the trial. Herbal medications cannot be taken within 7 days of randomisation (3 weeks for St John's wort) or throughout the course of the study.

Savolitinib-specific restrictions based on clinical pharmacology

- Savolitinib is a weak inhibitor of OATP1B1, OATP1B3 and BCRP. Discontinuation of statins is advised unless considered essential, in which case, the patient should be prescribed the lowest available dose and monitored for the effects of increased statin exposure.
- Savolitinib and its major metabolite, M2, are weak competitive inhibitors of CYP2C8 (IC_{50}= and μM, respectively). Those drugs defined as strong CYP2C8 substrates (almost exclusively metabolised by CYP2C8, such as Repaglinide and Rosiglitazone) should be used with caution.
- Savolitinib and its major metabolite, M2, are weak competitive inhibitors of CYP3A4/5 (IC_{50} = and μM, respectively). Concomitant use of CYP3A4 substrates which have a narrow therapeutic range or CYP3A4 sensitive substrates during the trial should be avoided as far as possible unless considered essential by the investigator, in which case patients must be monitored closely for potentially increased toxicity due to drug-drug interactions.
- Savolitinib is not a substrate of P-glycoprotein (Pgp) but is a weak inhibitor in vitro (IC_{50}= μM). Drugs that are known to be affected by Pgp such as digoxin, quinidine, loperamide, saquinavir and ritonavir should be used with caution.
- Savolitinib is an inhibitor of MATE1 and MATE2K (IC_{50} Metformin should be used with caution and patients monitored for the effect of increased metformin exposure.

7.7.3 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to the first subject randomised and any subsequent amendments will be documented, with final amendments completed prior to database lock. The aim of this study is to compare the efficacy and safety of savolitinib versus sunitinib. Analyses will be performed by AstraZeneca or its representatives. All personnel involved with the analysis of the study will remain blinded to aggregated results until database lock and protocol violators identified.

Due to termination of recruitment into SAVOIR, all secondary analyses will be descriptive.

Sample size estimate

Approximately 180 patients were planned to be randomised from 5 to 10 countries worldwide in approximately 50 to 75 sites. Recruitment to the study was closed on 22 November 2018. It is now estimated that approximately 50 patients will be randomised from 7 countries.

The initial assumption was that the true treatment effect had a hazard ratio (HR) of 0.6 (which would have translated to an approximate 3-month improvement in median PFS over an assumed 4-month median PFS for MET-driven patients on sunitinib, assuming PFS was exponentially distributed), 121 PFS events confirmed by BICR would have had to have been observed for the study to have 80% power to show a statistically significant difference in PFS at the two-sided 5% level. The smallest treatment difference that would have been statistically significant at the final analysis was a PFS HR of 0.69. Assuming 67% maturity; 180 patients would have been needed to be randomised. An interim futility analysis of PFS was planned to be conducted when a total of approximately 36 BICR-confirmed PFS events had been observed (30% of 121 PFS events, which was estimated to occur 17 months after the first patient had been randomised). Following IDMC endorsement to terminate recruitment into SAVOIR, the interim analysis will not occur.

[redacted]

[redacted]

Following IDMC endorsement to terminate recruitment into SAVOIR, a sample size-reassessment will no longer be performed.

8.2 Definitions of analysis sets

8.2.1 Full analysis set

The full analysis set (FAS) will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the ITT population. Therefore, all efficacy and HRQoL data will be summarised and analysed using the FAS on an ITT basis.

8.2.2 Safety analysis set

The safety analysis set consists of all patients who received at least one dose of randomised treatment (regardless of whether that was the randomised therapy intended or indeed whether, in rare cases, they received therapy without being randomised), according to the treatment they actually received. PRO CTCAE data will be summarised using the SAS.

8.2.3 PK analysis set

All patients who receive at least 1 dose of savolitinib per the protocol, for whom any post-dose PK data are available and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set. The population will be defined by the Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed. Where a protocol deviation impacts only part of a subject's data,

the affected portion of the subject's PK data will be excluded from PK analysis and summary statistics, and the remaining valid data will be utilised.

8.3 Outcome measures for analyses

8.3.1 Calculation or derivation of efficacy variables

8.3.1.1 Blinded Independent Central Review (BICR) of RECIST-based assessments

Review of radiological imaging data will be carried out using RECIST version 1.1. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to the sponsor-designated vendor by the site following completion of each scan. All scans will be read by BICR after notification of Progressive Disease by the investigator. If PD is not centrally confirmed, each subsequent scan will be read by BICR once it is received and processed by the sponsor-designated vendor. Once the institution calls PD, the scans will be reviewed by two independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. The radiologists will be blinded to treatment. Depending on the speed and completeness of image submission to the sponsor-designated vendor, the turn-around time should generally be within 10 days. All scans will be reviewed for the primary analysis even for the patients who do not have PD per local review.

For each patient, BICR will define the overall visit response data (CR, PR, SD, PD or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE).

8.3.1.2 Progression-Free Survival (PFS)

PFS is defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the subject withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment prior to the two missed visits.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

The primary analysis of PFS will be based on BICR; PFS per investigator review will be a sensitivity analysis.

8.3.1.3 Objective Response Rate (ORR)

ORR rate is defined as the number (%) of patients with measurable disease with at least one visit response of CR or PR. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response, which occurred after a further anticancer therapy was received, will not be included in the numerator for the ORR calculation.

Summaries of ORR will be based on BICR; ORR per investigator review will be a sensitivity analysis.

8.3.1.4 Duration of Response (DoR)

Duration of response will be defined as the time from the date of first documented response on study medication until the date of BICR-confirmed progression or death in the absence of disease progression. The end of the duration of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

Summaries of DoR will be based on BICR; DoR per investigator review will be a sensitivity analysis.

8.3.1.5 Disease control rate (DCR)

Disease control rate at 6 months is defined as the percentage of patients who have a best objective response of CR or PR in that period or who have demonstrated SD for a minimum interval of 24 weeks (minus 1 week to allow for an early assessment within the assessment window, ie, 161 days) following the date of randomisation. Disease control rate at 12 months is defined as the percentage of patients who have a best objective response of CR or PR in that period or who have demonstrated SD for a minimum interval of 48 weeks (minus 1 week to allow for an early assessment within the assessment window, ie, 329 days) following the date of randomisation.

Summaries of DCR will be based on BICR; DCR per investigator review will be a sensitivity analysis.

8.3.1.6 Tumour shrinkage

Tumour shrinkage will be assessed using RECIST tumour response. The absolute change and percentage change from baseline in sum of tumour size at each assessment will be calculated.

The best change in tumour size will include all assessments prior to progression or start of subsequent anticancer therapy.

Summaries of tumour shrinkage will be based on BICR; tumour shrinkage per investigator review will be a sensitivity analysis.

8.3.1.7 Overall Survival (OS)

OS is defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made within 5 days following the date of the data cut-off for each OS analysis, and if patients are confirmed to be alive, or if the death date is post the final data cut-off date, these patients will be censored at the date of the final data cut off. Death dates may be found by checking publicly available death registries.

8.3.1.8 Time to second progression or death (PFS2)

Time from randomisation to second progression or death is defined as the time from the date of randomisation to either the progression event after the start of a subsequent non-study anti-cancer therapy, or death. Determination of PD for second PFS on subsequent anti-cancer therapy will only be collected in those patients who had PD by RECIST 1.1 on study medication (investigator assessed). The date of second progression will be recorded by the investigator and defined according to local standard clinical practice. The date of each scan evaluating tumour response on subsequent therapy and the investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the electronic case report form (eCRF). The site staff should review second progression status and record all subsequent therapy at least every 12 weeks following study medication discontinuation. Patients who are alive and for whom a second disease progression (PFS2) has not been observed should be censored at the last time known to be alive and without a second disease progression, ie, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

8.3.1.9 HRQoL and symptoms

Patient reported outcomes will be assessed using the FACIT-F and FKSI-19 questionnaires. An outcome variable consisting of a score calculated using respective scoring manuals will be derived for each of the symptom scales/symptom items of these questionnaires. Higher scores on the global health status and functioning scales indicate better health status/function. Higher scores on the symptoms scales indicate greater symptom burden (see Section 5.3.1 for more details). PRO-CTCAE will be analysed descriptively since it is an exploratory endpoint.

8.4 Methods for statistical analyses

All efficacy analyses will be performed on the FAS populations. Results of all statistical analyses will be presented using a 95% confidence interval and 2-sided p-value.

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total and for each treatment group.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of investigational product, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomisation.

Efficacy and HRQoL data will be summarised based upon the FAS analysis set. Safety and treatment exposure data will be summarised based upon the safety analysis set by actual treatment received. Study population and demography data will be summarised based upon the FAS analysis set.

8.4.1 Analysis of the primary variable (s)

The log-rank test will be stratified by IMDC risk group (poor, intermediate, favourable) and line of therapy (1st line; previously treated with an anti-VEGF TKI; previously treated without an anti-VEGF TKI) providing there are at least 10 PFS events within each strata. If not, then the log-rank test will be stratified by IMDC risk group only, providing there are at least 10 PFS events within each strata. If not, then the log-rank test will be unstratified.

The effect of treatment will be estimated by the HR together with its corresponding 95% CI and p-value. Kaplan Meier plots will be provided.

8.4.2 Analysis of the secondary variable(s)

Objective Response and Disease Control Rates

ORR and DCR will be presented with a two-sided 95% CIs using Clopper-Pearson method (Clopper and Pearson, 1934). The number and percentage of patients in each response category (CR, PR, SD, PD, NE) will be summarised. Results may be summarised by the IMDC risk category if patient numbers permit.

Duration of response

Kaplan-Meier plots of duration of response in the responding patients will be produced.

Change in tumour size

The best change in target lesion tumour size from baseline (where best change in target lesions size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction) will also be summarised.

Waterfall plots (bar charts) indicating the best percentage change from baseline in sum of the diameters of TLs will be produced. Reference lines at the +20% and 30% change in tumour size levels will be added to the plots, which correspond with the definitions of progression and 'complete or partial' response respectively.

Overall Survival

Summaries (number of deaths, medians, and proportion alive at 1 year) and Kaplan Meier plots will be provided.

Time to second progression or death (PFS2)

Summaries (number of 2nd progression events or deaths, medians, and proportion alive at 1 year) and Kaplan Meier plots will be provided.

PRO analyses

Analyses on the FACIT-F, FKSI-19, EQ-5D-5L and PRO-CTCAE will be based on the instruments' scoring manuals.

Descriptive statistics will be calculated for each scheduled visit/time point in the study, for each trial arm and as a total. These will report the number of patients, the number of EQ-5D questionnaires completed at each visit, the number and proportion responding to each dimension of the EQ-5D-5L. Additionally, summary statistics (eg, n, mean, median, sd, min, max) will be reported for the EQ-5D index score and the EQ-VAS score, and the change from baseline for the EQ-5D index score and the EQ-VAS score.

To support submissions to payers, additional analyses may be undertaken and these will be outlined in a separate Payer Analysis Plan.

Safety analyses

Safety data will not be analysed formally. Standard data summaries will be produced for safety data including (but not limited to):

- Summaries of AEs of any CTCAE grade – summarised by MedDRA preferred term and system organ class and CTCAE grade.
- Summaries of Grade 3 and above AEs.
- SAEs.

- Any AE occurring within the defined 30 day follow up period after discontinuation of investigational product will be included in the AE summaries.
- Deaths will be summarised by primary cause, along with AEs with an outcome of "fatal".
- Haematology, clinical chemistry, vital signs, ECG, ECHO/MUGA data and concomitant medication will be summarised.
- Any qualitative safety assessments for urinalysis will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration, or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared with baseline.

8.4.3 Subgroup analysis

No subgroup analysis will be performed.

8.4.4 Interim analysis

An interim futility analysis of PFS was planned to be conducted when a total of approximately 36 PFS events confirmed by BICR had been observed (30% of 121 PFS events, which was estimated to occur 17 months after the first patient had been randomised). Following IDMC endorsement to terminate recruitment into SAVOIR, the interim analysis will not occur.

8.4.5 Sensitivity analysis

Investigator assessment:

PFS will be reported per investigator assessment.

8.4.6 Exploratory analyses

8.4.6.1 Pharmacokinetics

The savolitinib plasma concentration data obtained from the samples collected in this study may be included in the listings of the CSR but these data will be pooled with data from other studies in order to perform a population PK analysis. The results of this analysis will be reported in a separate population PK report.

8.4.6.2 Pharmacogenetic research and statistical methods, and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC and ePRO systems utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study medication accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement (CSA) for location of source data.

9.2.2 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement (CSA), or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last clinic visit of the last subject undergoing the study'.

The final analysis of all endpoints will be conducted at the earliest time when the following 2 criteria are met:

1 36 PFS events by investigator assessment
2 The opportunity to have at least 7.5 months follow-up from randomisation

If criterion #1 has not been met 12 months after last subject in, the final analysis will be performed.

At this time point, the clinical study database will close to new data.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with savolitinib.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre according to the Data Management Plan. The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications

will be classified according to the WHO Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process. When all data have been coded, validated, and locked, clean file will be declared.

9.4.1 Serious Adverse Event (SAE) reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

9.4.2 Data management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

9.4.3 Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

9.4.4 Management of external data

Data Management determines the format of the data to be received from external providers and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (eg, eDiary, IVRS/IWRS, etc.) will be tested/validated as needed. Data from external providers will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database.

In the case of [redacted] data, the results of any analyses will not be recorded in the database, but information relating to the processing of the sample, including the original date of [redacted] and the actual date the sample(s) were collected) will be recorded in the eCRF and database.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee (EC) or Institutional Review Board (IRB) should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the EC/IRB annually.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs/IRBs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the ECs/IRBs with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure that each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Forms are stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the subject.
- Ensure that any incentives for patient who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee or Institutional Review Board.

The genetic research is optional, in countries where applicable, and the patient may participate in the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the genetic aspect of the study at any time.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed by AstraZeneca without consulting of the International Co-ordinating Investigator.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee or Institutional Review Board and if applicable, also by the national regulatory authority, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee/Institutional Review Board see Section 10.3.

If amended change to a Clinical Study Protocol requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee/Institutional Review Board are to approve the revised Informed Consent Form before the revised form is used.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

Armstrong et al 2016
Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multi-centre, openlabel, randomised phase 2 trial. Lancet Oncol. 2016;17(3):378-88.

Basch et al 2009
Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst. 2009;101(23):1624-32.

Bellmunt and Dutcher 2013
Bellmunt J, Dutcher J. Targeted therapies and the treatment of non-clear cell renal cell carcinoma. Ann Oncol. 2013;24(7):1730-40.

Choueiri et al 2013
Choueiri TK, Vaishampayan U, Rosenberg JE, Logan TF, Harzstark AL, Bukowski RM, et al. Phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. J Clin Oncol. 2013;31(2):181-6.

Clopper and Pearson, 1934
Clopper C and Pearson E. S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-413.

Escudier et al 2014
Escudier B, Porta C, Schmidinger M, Algaba F, Patard JJ, Khoo V, et al. ESMO Guidelines Working Group. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii49-56.

Fischer et al 1998
Fischer J, Palmedo G, von Knobloch R, Bugert P, Prayer-Galetti T, Pagaono F, et al. Duplication and overexpression of the mutant allele of the MET proto-oncogene in multiple hereditary papillary renal cell tumours. Oncogene. 1998;17(6):733-9.

Gan et al 2015
Gan HK, Lickliter J, Millward M, Gu Y, Weiguo S, Qi C, et al. cMet: Results in papillary renal cell carcinoma of a phase I study of AZD6094/volitinib leading to a phase 2 clinical trial with AZD6094/volitinib in patients with advanced papillary renal cell cancer (PRCC). J Clin Oncol 33, 2015 (suppl 7; abstr 487).

Grubb et al 2007
Grubb RL 3rd, Franks ME, Toro J, Middelton L, Choyke L, Fowler S, et al. Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. J Urol. 2007;177(6):2074-9; discussion 2079-80.

Jeffers et al 1997
Jeffers M, Schmidt L, Nakaigawa N, Webb CP, Weirich G, Kishida T et al. Activating mutations for the met tyrosine kinase receptor in human cancer. Proc Natl Acad Sci USA. 1997;94(21):11445-50

Klatte et al 2009
Klatte T, Pantuck AJ, Said, JW, Seligson DB, Rao NP, La Rochelle JC et al. Cytogenetic and molecular tumour profiling for type 1 and type 2 papillary renal cell carcinoma. Clin Canc Res. 2009;15(4):1162-9.

Kovacs 1993
Kovacs G. Molecular cytogenetics of renal cell tumours. Advanced Can Res 1993;62:89-124.

Kroeger et al 2013
Kroeger N, Xie W, Lee JL, Bjarnason GA, Knox JJ, Mackenzie MJ, et al. Metastatic non-clear cell renal cell carcinoma treated with targeted therapy agents: characterization of survival outcome and application of the International mRCC Database Consortium criteria. Cancer. 2013;119(16):2999-3006.

Linehan et al 2012
Linehan WM. Genetic basis of kidney cancer: role of genomics for the development of disease-based therapeutics. Genome Res. 2012;22(11):2089-100.

Litwin et al 1999
Litwin MS, Lubeck DP, Henning JM, et al. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: Results of the CaPSURE database. J Urol. 1998;159(6):1988-92.

Ljungberg et al 2011
Ljungberg B, Campbel SC, Cho HY, Jacqmin D, Lee JE, Weikert S, et al. The epidemiology of renal cell carcinoma. Euro Urol. 2011;60(4):615-21.

Ljungberg et al 2015
Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67(5):913-24.

Motzer et al 2002
Motzer RJ, Bacik J, Mariani T, Russo P, Mazumdar M, Reuter V. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. J Clin Oncol. 2002;20(9):2376-81.

Motzer et al 2015
Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol. 2015;16(15):1473-82.

NCCN; v. 2.2017, dated October 31, 2016
National Comprehensive Cancer Network. Kidney Cancer (Version 2.2017; dated October 31, 2016). URL: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

New York Heart Association 1994
The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-56.

Rao et al 2009
Rao D, Butt Z, Rosenbloom S, Robinson D, Von Roenn J, Kuzel TM, et al. A comparison of renal cell carcinoma symptom index (RCC-SI) and the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI). J Pain Symptom Manage. 2009;38(2):291-8.

Schmidt et al 1997
Schmidt L1, Duh FM, Chen F, Kishida T, Glenn G, Choyke P. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet. 1997;16(1):68-73.

Siegel RL, Miller KD, Jemal A. 2016
Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2016. CA Cancer J Clin. 2016; 66:7-30.

Sprangers et al 1992
Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: A review. J Clin Epidemiol. 2002;55(11):1130-43.

Sweeney et al 2002
Sweeney P, El-Naggar AK, Lin SH, Pisters LL. Biological significance of c-met over expression in papillary renal cell carcinoma. J Urol. 2002;168(1):51-5.

Tannir et al 2015
Tannir NM, Jonasch E, Albiges L, Altinmakas E, Ng CS, Matin SF, et al. Systemic Therapy for Non–clear Cell Renal Cell Carcinomas: Everolimus Versus Sunitinib Prospective

Evaluation in Metastatic Non–Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial. Eur Urol. 2016;69(5):866-74.

The Cancer Genome Atlas Research Network 2016
Linehan WM, Spellman PT, Ricketts CJ, Creighton CJ, Fei SS, Davis C, et al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. N Engl J Med. 2016;374:135-45.

Vera-Badillo et al 2015
Vera-Badillo FE, Templeton AJ, Duran I, Ocana A, de Gouveia P1, Aneja P, et al. Systemic Therapy for Non–clear Cell Renal Cell Carcinomas: A Systematic Review and Meta-analysis. Eur Urol. 2015;67(4):740-9.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring i.v. hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation.

Development of drug dependency or drug abuse

A Guide to interpreting the causality question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B.
- are to be packed in accordance with UN3373 and IATA 650.

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Genetic Research

Rationale and objectives

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research plan and procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted blood products within 120 days of genetic sample collection.

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.10 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from subjects on Day 1, Cycle 1. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE); such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn on Day 1, Cycle 1, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood ample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the

subject understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organisation or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

Appendix D Acceptable Birth Control Methods

Patients and their partners, who are sexually active and of childbearing potential, must agree to the use of highly effective forms of contraception [as listed below], throughout the period of study treatment or they must totally/truly abstain from any form of sexual intercourse (see below), when this is in line with their preferred and usual lifestyle. Patients on savolitinib must continue contraception for at least 1 month (female patients) and 6 months (male patients) after their last dose.

Acceptable Non-hormonal birth control methods include:

- Total sexual abstinence (when this is in line with the preferred and usual lifestyle). Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose of savolitinib for females and for at least 6 months after the last dose of savolitinib for males. Periodic abstinence (eg, calendar ovulation, sympto-thermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom with spermicide.
- Intra-uterine device (IUD) PLUS male condom with spermicide. Provided coils are copper-banded.
- Acceptable hormonal methods:
- Normal and low dose combined oral pills PLUS male condom with spermicide.
- Etonogestrel implants (eg, Implanon, Norplan) PLUS male condom with spermicide.
- Norelgestromin / Ethinyl Estradiol (EE) transdermal system PLUS male condom with spermicide.
- Intravaginal device (eg, EE and etonogestrel) PLUS male condom with spermicide.
- Cerazette (desogestrel) PLUS male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.
- Intrauterine system [IUS] device (eg, levonorgestrel releasing IUS - Mirena®) PLUS male condom with spermicide.
- Hormonal shot or injection (eg, Depo-Provera) PLUS male condom with spermicide.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the management of liver abnormalities can be found in Section 6.8.1.2 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events. These include samples taken at scheduled study visits and other visits including central and all local laboratory evaluations, even if collected outside of the study visits. For example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review adverse event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator will participate, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and Serious Adverse Events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3xULN **together with** TBL ≥2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative.
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

Follow-up:

Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For patients that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change* in the patient's condition.

The AstraZeneca Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Complete the follow-up SAE form as required.
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the AstraZeneca Study Physician.
- Complete the three Liver eCRF Modules as information becomes available.

Review and assessment of potential Hy's Law cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the AstraZeneca Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from the date that the PHL criteria were met. The AstraZeneca Global Clinical Lead (or equivalent) and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, update the previously-submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term, causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously-submitted SAE of 'Potential Hy's Law' (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously-submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease?

If No: follow the process for reporting PHL as an SAE, described in "Potential Hy's Law criteria met" of this Appendix.

If Yes:

Determine if there has been a significant change in the patient's condition* compared with when PHL criteria were previously met:

- If there is no significant change no action is required.
- If there is a significant change, follow the process for reporting PHL as an SAE, described in "Potential Hy's Law criteria met" of this Appendix.

* A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the AstraZeneca Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix F Guidance for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

F 1 INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D5082C00003 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

F 2 DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Patients with at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT/MRI and is suitable for repeated assessment will be entered in this study.

Measurable:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

1 All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline*).
2 Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
3 Previously irradiated lesions.**
4 Skin lesions assessed by clinical examination.
5 Brain metastases.

* Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Special Cases:

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient; these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

F 3 METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterise each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table F1 Summary of Methods of Assessment

Target lesions	Non-target lesions	New lesions
CT(preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical Examination	Clinical Examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone scan
		FDG-PET

F 3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D5082C00003 study it is recommended that CT examinations of the chest*, abdomen and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

1 *Chest, abdomen and pelvis CT/MRI scans should be performed at baseline.
2 *In those patients with thoracic lesions or upper abdomen lymphadenopathy identified at baseline assessment, chest, abdomen and pelvis should be performed at follow-up.
3 *In those patient with no disease present in the chest and no upper abdomen lymphadenopathy then follow-up is by abdomen and pelvis only.

F 3.2 Clinical examination

Clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

F 3.3 X-ray

Chest X-ray

Chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

F 3.4 Ultrasound

Ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

F 3.5 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments, as they are not validated in the context of tumour assessment.

F 3.6 Tumour markers

Tumour markers will not be used.

F 3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

F 3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

F 3.9 FDG-PET scan

FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

F 4 TUMOUR RESPONSE EVALUATION

F 4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before randomisation, and ideally should be performed as close as possible to the start of study treatment. Follow-up assessments will be performed every 6 weeks at the start of each cycle (±7 days), for the first year, then every 12 weeks (±1 week) relative to the date of randomisation, until objective disease progression as defined by RECIST 1.1. See Table 1 Study Schedule from Study Protocol for further information. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

F 4.2 Target lesions (TL)

F 4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected. The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

1 For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis. If the CT/MRI slice thickness used is >5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
2 If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
3 If a TL splits into two or more parts, then record the sum of the diameters of those parts.

4 If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

5 If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.

6 If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

7 When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

F 4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table F2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

F 4.3 Non-target lesions (NTL)

F 4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table F3 Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or, some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit.

Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

F 4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

F 4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

F 4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table F4.

Table F4 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR / Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD nor NE	No	SD
NA	Non CR / Non PD	No	SD (Non CR / Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = not evaluable, NA = not applicable (only if relevant if there were no TL/NTL at baseline)

F 5 CENTRAL REVIEW

The Contract Research Organisation (CRO) appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

F 6 REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-24

Appendix G Performance Status (Karnofsky Scale)

Table G1 Example of Performance Status (Karnofsky Scale)

Description	ECOG grade	Karnofsky Scale	
Fully active, able to carry on all pre-disease performance without restriction.	0	100	Normal, no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework, office work.	1	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self but unable to carry on normal activity or to do work.
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	60	Requires occasional assistance but is able to care for most of personal needs.
		50	Requires considerable assistance and frequent medical care.
Capable of only limited self care, confined to bed or chair more than 50% of waking hours.	3	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalisation is indicated although death not imminent.
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4	20	Very ill; hospitalisation and active supportive care necessary.
		10	Moribund.

Appendix H Guidance Regarding Potential Interactions of Savolitinib with Concomitant Medications

There is currently no clinical data which suggests that there is a PK interaction between savolitinib and any concomitant medications.

Based upon studies of *in vitro* liver microsomes and S9 fractions, savolitinib is metabolised by several metabolic enzymes, including both CYP450 enzymes and some NADPH-independent non-CYP enzymes.

Concomitant use of drugs that are known to be CYP3A4 substrates of narrow therapeutic range or CYP3A4 sensitive substrates during the trial should be avoided as far as possible unless considered essential by the Investigator, in which case patients must be monitored closely for increased toxicity due to drug-drug interactions.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to potently modulate CYP3A4 or CYP1A2 activity. If required, please refer to full prescribing information for all drugs prior to co-administration with savolitinib.

In vitro transporter data have predicted that there is a possibility that savolitinib and/or its major metabolite M2 inhibit the human efflux transporter breast cancer resistant protein (BCRP, ABCG2), and the hepatic uptake transporters organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3). These findings plus data on cytochrome CYP3A4 inhibition suggest an increased chance of a clinically relevant drug-drug interaction (DDI) between savolitinib and any co-administered drug that is a substrate for these transporters including statins. There is the potential for several-fold over exposure of statins in patients taking standard doses of statins in addition to savolitinib. Therefore, use of statins should be avoided as far as possible and, if considered necessary, the patients should be given the lowest available dose and closely monitored for the effects of increased statin exposure.

In addition, savolitinib and M2 also inhibit multidrug and toxin extrusion proteins 1 (MATE1, SLC47A1) and 2K (MATE2K, SLC47A2) leading to an increased chance of a clinically relevant DDI between savolitinib and any co-administered drug that is a substrate for these transporters including metformin. Thus, metformin should be used with caution in case of potential increased metformin exposure.

For both savolitinib and sunitinib: Table H1 provides a list of potent inducers of CYP3A4. Tables H2 and H3 provides a list of potent inhibitors of CYP3A4 and CYP1A2. Table H4 provides a list of CYP3A4 substrates which have a narrow therapeutic range and Table H5 provides a list of CYP3A4 sensitive substrates. Patients receiving or unable to discontinue potent inducers of CYP3A4 or potent inhibitors of CYP3A4 or CYP1A2 for 2 weeks before

the date of randomisation (3 weeks for St John's Wort) are excluded from enrolment in the study.

Table H1 Drugs known to be strong inhibitors of CYP3A4

Potent inhibitors of CYP3A4 enzymes
boceprevir
clarithromycin
conivaptan
cobicistat
danoprevir
elvitegravir/ RIT
fluconazole
grapefruit and grapefruit juice[a]
indinavir
itraconazole
ketoconazole
lopinavir/ritonavir
LCL161
mibefradil
nefazodone
nelfinavir
posaconazole
ritonavir
saquinavir
telaprevir
telithromycin
tipranavir/RIT
troleandomycin
voriconazole

[a] Patients should abstain from eating grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study

Table H2 Drugs known to be strong inducers of CYP3A4

Potent Inducers of CYP3A4
avasimibe
carbamazepine
enzalutamide
mitotane
phenobarbital
phenytoin
rifabutin
rifampin
St. John's Wort

Table H3 Drugs known to be strong inhibitors of CYP1A2

Potent inhibitors of CYP1A2 enzymes which may increase exposure to savolitinib
fluvoxamine
ciprofloxacin
enoxacin

Table H4 Drugs known to be CYP3A4 substrates with a narrow therapeutic range

CYP3A4 substrates know to have a narrow therapeutic range
alfentanil
cyclosporine
diergotamine
ergotamine
fentanyl
pimozide
quinidine
sirolimus
tacrolimus

Table H5 Drugs known to be CYP3A4 sensitive substrates

CYP3A4 sensitive substrates
alfentanil
almorexant
alpha-dihydroergocryptine
aplaviroc
aprepitant
atazanavir
atorvastatin
avanafil
BIRL 355
bosutinib
brecanavir
brotizolam
budesonide
buspirone
capravirine
casopitant
conivaptan
danoprevir
darifenacin
darunavir
dasatinib
dronedarone
ebastine
eletriptan
elvitegravir
eplerenone
everolimus
felodipine
ibrutinib
indinavir
ivacaftor
L-771,688
levomethadyl (LAAM)
lomitapide

Table H5 Drugs known to be CYP3A4 sensitive substrates

CYP3A4 sensitive substrates
lopinavir
lovastatin
lumefantrine
lurasidone
maraviroc
midazolam
midostaurin
neratinib
nisoldipine
perospirone
quetiapine
ridaforolimus
saquinavir
sildenafil
simeprevir
simvastatin
sirolimus
tacrolimus
terfenadine
ticagrelor
tilidine
tipranavir
tolvaptan
triazolam
vardenafil
vicriviroc
voclosporin

Savolitinib is a weak competitive inhibitor of CYP2C8 (IC_{50}=9.1µM). Those drugs defined as potent 2C8 substrates (almost exclusively metabolised by 2C8, such as Repaglinide, Dasabuvir and Rosiglitazone) should be used with caution.

Savolitinib is not a substrate of P-glycoprotein (Pgp) but is a weak inhibitor in vitro (IC_{50}=17.9 uM). Drugs that are known to be affected by Pgp such as digoxin, quinidine, loperamide, saquinavir and ritonavir should be used with caution.

Appendix I Guidance Regarding Potential Interactions of Savolitinib with Concomitant Medications Known to Prolong QT Interval

Drugs that prolong QT interval

The drugs listed in this section are taken from information provided by the Arizona Center for Education and Research on Therapeutics website (available at URL: https://www.crediblemeds.org). The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website above.

Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended (Table I1). These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in the table below and should not be co-administered with savolitinib and for a period of one week after discontinuing study treatment. The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the website to provide the most up to date information.

Table I1 Drugs with known risk of TdP

Drugs with a known risk of TdP	
Drug name	**Withdrawal period prior to study treatment start**
Anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin	2 days
Cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide*, ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

Appendix J Patient Reported Outcomes

DISEASE RELATED SYMPTOM QUESTIONNAIRE

Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19) to be administered to patients in Stage 1 and Stage 2

NCCN-FACT FKSI-19

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	HI12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
DRS-E	GF5	I am sleeping well	0	1	2	3	4
	GB6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)

03 March 2010
Page 1 of 1

HEALTH RELATED QUALITY OF LIFE QUESTIONNAIRE

FACIT-F (Version 4) to be administered to patients in the Main Study.

FACIT-F (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACIT-F (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACIT-F (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

HEALTH UTILITY QUESTIONNAIRE

EuroQol Group. EQ-5D™ v.2 © 2009 is to be administered to patients in Stage 2.

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework,* family or leisure activities)

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

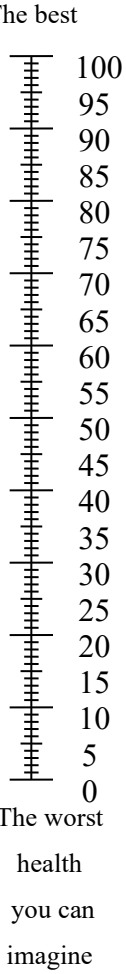
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



NCI PRO-CTCAE™ ITEMS (Item Library Version 1.0)

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

3.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

4.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				

	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

6.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

7.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

8.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST?				

	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

11.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

12.	In the last 7 days, what was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

13.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

14.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

15.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

16.	In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)?	
	○ Yes	○ No

Do you have any other symptoms that you wish to report?

○ Yes ○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Appendix K Stages of Heart Failure – New York Heart Association Classification

The Stages of Heart Failure – New York Heart Association Classification

Class I (Mild)

No Limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).

Class II (Mild)

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.

Class III (Moderate)

Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnoea.

Class IV (Severe)

Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, physical discomfort is increased.

Reference

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston (MA): Little, Brown & Co; 1994:253-256.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d5082c00003-csp-v6-redacted		
Document Title:	D5082C00003 Clinical Study Protocol version 6 Redacted	
Document ID:	Doc ID-004214947	
Version Label:	1.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
03-Mar-2020 14:22 UTC	Michael Tracy C	Content Approval
25-Feb-2020 13:42 UTC	Mireille Cantarini	Author Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.