Clinical Study Protocol	
Study Intervention	AZD8853
Study Code	D9450C00001
Version	3.0
Date	11 Apr 2022

A Phase I/IIa First-in-human, Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of AZD8853 in Participants with Selected Advanced/Metastatic Solid Tumours

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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.

Protocol Number: D9450C00001

Amendment Number: 2

Study Intervention: AZD8853

Study Phase: I/IIa

Short Title: A First-in-human Study to Evaluate the Safety and Tolerability of AZD8853 in Participants with Selected Advanced/Metastatic Solid Tumours

Study Physician Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	11-Apr-2022
Amendment 1	03-Dec-2021
Original Protocol	15-Oct-2021

The summary of changes for Amendment 2 is provided below. Refer to Appendix K for a summary of the previous amendments.

Amendment 2 11 April 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of European Union.

Overall Rationale for the Amendment:

The primary reasons for this protocol amendment were to update the definition of study population and the removal of prospective GDF15 testing/pre-screening. In addition, to implement changes based on template requirements and other updates to aid sense and flow of the document.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 (Synopsis; Key objectives and Endpoints Applicable to all Substudies) & Section 3 (Objectives and Endpoints)	Updated secondary efficacy endpoint description for change in ctDNA levels between baseline and post-treatment.	Clarification of secondary efficacy endpoint description for change in ctDNA levels from baseline to between baseline and post-treatment.	Non-substantial
Section 1.1 (Synopsis; Overall Design) & Section 10.4.1 (Substudy 1 Design)	Updated the definition for selected advanced/metastatic solid tumours from second to fourth line setting to second or later line setting of unresectable, locally advanced (Stage III) or metastatic (Stage IV) NSCLC that have progressed on anti-PD-1/PD-L1 inhibitors	Criteria adjusted for clarity, consistency, and to relax the criteria considering the study phase and population.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	with or without platinum-containing chemotherapy.		
Synopsis 1.2 (Schema, Figure 2) & Section 10.1.1 (Schema, Figure 3)	Removal of description requiring selection of participants with high GDF15 levels.	New data shows that up to CCI % of the study participants may have high GDF15 levels (above the current cut off); in addition, the removal of the GDF15 cut off level does not have any impact on participant safety.	Substantial
Section 1.1 (Synopsis; Overall Design; Table 2) & Section 10.4.1 (Substudy 1 Design)	Updated the number of participants required for Part B1 and B2 to "approximately" 10 MSS-CRC and "approximately" 10 NSCLC participants for PD cohort and "up to" 10 participants for CD8+ PET cohort.	Clarification on the number of participants required for Part B1 and B2.	Non-substantial
Main study			
Section 2.1 (Study Rationale)	Removal of description requiring selection of participants with high GDF15 levels.	New data shows that up to CCI % of the study participants may have high GDF15 levels (above the current cut off); in addition, the removal of the GDF15 cut off level does not have any impact on participant safety.	Substantial
Section 2.2.1 (Tumour Selection Type)	Updated text to include information from ongoing trials suggesting CCI % of pre-treated patients in these indications have CCI GFD15 levels.	Clarification and further information regarding background to tumour selection.	Non-substantial
Section 4.2 (Scientific Rationale for Study Design), Section 5.1 (Inclusion Criteria), old section 5.4 (Pre-Screen and Screen Failures),	Removal of description requiring pre-screening for GDF15 levels.	New data shows that up to CCI % of the study participants may have CCI GDF15 levels (above the current cut off); in addition, the removal of the GDF15 cut off level does not	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 6.3 (Measures to Minimise Bias: Randomization and Blinding), Section 6.5 (Concomitant Therapy), and Section 8 (Study Assessments and Procedures)		have any impact on participant safety.	
Section 4.4 (End of Study Definition)	Deletion of definition for completion of study.	The study design does not allow participants to be considered completed.	Non-substantial
Section 5.1 (Inclusion Criteria)	Criterion 8, addition of the Cockcroft-Gault formula for calculating creatinine clearance.	Since creatinine clearance is included as an inclusion criterion, its calculation needs to be standardized for collection in eCRF.	Non-substantial
Section 5.2 (Exclusion Criteria)	Criterion 10, updated to exclude body weight loss > 10% within 30 days of screening.	Clarification of language regarding inclusion of participants with body weight loss.	Non-substantial
	Criterion 20, deletion of old bullet a) related to previous suspected or confirmed COVID-19 diagnosis.	Clarification of language regarding inclusion of participants with prior COVID-19.	Non-substantial
	Criterion 20, updates made to old bullet b) now a) in relation to COVID-19 cases prior to Cycle 1 Day 1.	Clarification of language regarding inclusion of participants with prior COVID-19.	Non-substantial
Section 5.3.2 (Activity)	Text updated to clarify that strenuous exercise is not allowed 48 hours prior to each GDF15 blood collection.	Clarification that this restriction applies only to visits with GDF15 blood collection.	Non-substantial
Section 6.5 (Concomitant Therapy)	Update to Table 8 for prohibited concurrent chemotherapy during the study.	Clarification that concurrent use of hormones for non-cancer-related conditions and local treatment of isolated lesions may be acceptable upon consultation with study physician.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Update to Table 8 for prohibited metformin use during the study.	Based on available research data, CCI [redacted]	Substantial
Section 6.5.1 (Rescue Medicine) & Section 10.6.6 (Rescue Medication)	Deletion of this template section for rescue medicine.	Rescue medicine is not specified for this study.	Substantial
Section 8.1 (Efficacy Assessments, Skeletal Muscle Index)	Updated text for CT or MRI scans that will be obtained for SMI assessment.	Clarification that CT or MRI scans for SMI assessment will be obtained using the same modality and timepoints as the disease assessment scans.	Non-substantial
Section 8.2.1 (Physical Examinations)	Text has been added to categorise participants appetite as poor, average, or good and change in appetite as worse, about the same, or improved.	Clarification of data to be collected in eCRF.	Non-substantial
Section 8.2.5 (Clinical Safety Laboratory Assessments)	Deletion of time of collection from text.	Clarification of local laboratory assessment needs.	Non-substantial
	Table 10, deletion of carbonate and phosphate from clinical chemistry variable list. The addition of lactate dehydrogenase.	Clarifications of local laboratory assessment needs.	Non-substantial
	Table 10 addition of a footnote microscopy.	Clarification that it is investigator discretion for microscopy for abnormal dipstick results.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.3.1 (Time Period and Frequency for Collecting AE and SAE Information)	Addition of text for collection of any SAE, including death, at any time during survival follow-up that is suspected to have a causal relationship to study intervention.	Clarifications of local laboratory assessment needs.	Non-substantial
Section 8.3.9 (Disease Under Study)	This section is deleted.	To prevent duplication and aid clarity, AEs reporting for disease under study is already covered in Section 8.3.5.	Non-substantial
Section 8.4 (Overdose)	Updated time window for reporting relevant information to AstraZeneca Patient Safety within 1 to 5 days for overdose associated SAEs.	Clarification of time window to between 1 and 5 days from 1 or 5 days.	Non-substantial
Section 9.6 (Safety Review Committee)	Updated text for SRC required data, confirming that every effort is to be made to provide available PK data for SRC meetings.	Clarification that PK data is not a requirement for SRC meetings but every effort should be made to provide available PK data.	Non-substantial
Substudy 1			
Section 10.1.2 (Schedule of Activities, Table 12)	Removal of pre-screening for GDF15 levels ≥ CCI pg/mL.	New data shows that up to CCI % of the study participants may have CCI GDF15 levels (above the current cut off); in addition, the removal of the GDF15 cut off level does not have any impact on participant safety.	Substantial
	Assignment of participant identification number, metformin use history, and demographic information moved to screening.	Updated as required following the removal of pre-screening visit.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Addition of Part A/C [redacted] and Part B mandatory paired biopsy at screening. Addition of new footnote e stating that if they are taken during screening they will not need to be taken for Cycle 1 Day 1 pre-dose.	Clarification of the time window for collection of paired biopsies.	Non-substantial
	Updated footnote b to include CT or MRI scans for SMI assessment.	Updated for consistency with updates in Section 8.1.	Non-substantial
	Deletion of old footnote e)	To prevent repetition, the detailed description of archival tissue block collection is only included in Section 10.8.6.2.	Non-substantial
	Addition to footnote f) stating that the if participants hold or discontinue treatment prior to Day 29, they should still perform PET scan if they are able.	Clarification of collection requirements.	Non-substantial
Section 10.1.2 (Schedule of Activities, Table 13)	Included new footnote a confirming safety assessments are relative to most recent dosing.	Clarification of collection requirements.	Non-substantial
	Updated time windows for disease assessments to include ±1D for V4 to V8, and ±3D for V12 and V13+.	Added ±1 and ±3 day windows to be consistent with prior collection timepoints.	Non-substantial
	Updated time window for disease assessment at V8/V9 and V12.	Clarification of time window for disease assessment.	Non-substantial
	Updated footnote d (now e) to include CT	Updated for consistency with updates in Section 8.1.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	or MRI scans for SMI assessment.		
	Updated footnote k (now l) for paired biopsies stating if they are taken during screening they will not need to be taken for Cycle 1 Day 1 pr-dose.	Clarification that [redacted] If they are collected during screening period, they do not need to be collected pre-dose Cycle 1 Day 1.	Non-substantial
	Updated footnote l (now m) time window for second biopsy sample to [redacted] days relative to Cycle 2 Day 8.	Shortened time window for second biopsy in order to reduce variability between subjects and for correlative analysis with CD8+ PET.	Non-substantial
	Addition to footnote n (now o) stating that if participants hold or discontinue treatment prior to Day 29, they should still perform PET scan if they are able.	Clarification of collection requirements.	Non-substantial
Section 10.1.2 (Schedule of Activities, Table 14)	Updated footnote a to include CT or MRI scans for SMI assessment.	Updated for consistency with updates in Section 8.1.	Non-substantial
Section 10.4.1 (Substudy 1 Design)	Updated text for expected number of participants in the CD8+ PET cohort from Parts B1 and B2 to approximately 20, and that sites should prioritize recruitment to the CD8+ PET cohort of Part B prior to non-CD8+ sites.	Clarification of participant numbers and to reduce duplication of information provided in schedule of assessments.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 10.5 (Substudy 1 Population)	Removal of screening description from informed consent signing.	Clarification of informed consent to be signed.	Substantial
Section 10.5.1 (Substudy 1 Inclusion Criteria)	Update to criterion 2 for tumour-specific requirements in NSCLC, MSS-CRC, and UC.	Improve clarity of criteria and to improve enrolment.	Substantial
	Deletion of old criterion 3 for centrally confirmed pre-treatment GDF15 levels ≥ CCI pg/mL.	New data shows that up to CCI % of the study participants may have CCI GDF15 levels (above the current cut off); in addition, the removal of the GDF15 cut off level does not have any impact on participant safety.	Non-substantial
	Addition of new criterion 3 confirming that participation in this trial is determined to be the best option for next treatment option based on prior response to standard of care.	Clarification of criteria considering the study phase.	Non-substantial
	Updated criterion 4 to reduce the detail and refer to Section 10.8.6.2 and laboratory manual.	To prevent repetition, the detailed description of archival tissue block collection is only included in Section 10.8.6.2.	Non-substantial
Section 10.6.6.1.1. (Starting Dose)	Updated text to remove “single sentinel” from starting dose description.	Clarification of starting dose and process for dosing of participants in the first cohort.	Non-substantial
Section 10.6.10 (Definition of DLT Evaluable Participant)	Updated text to state that participants who do not remain in the	Clarification of definition of DLT evaluable participant.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	study up to the DLT evaluation period will be considered non-evaluable for DLT assessment.		
Section 10.8 (Substudy 1 Study Assessments and Procedures), Section 10.8.5.3 (GDF15 Assay for Prospective Testing)	Removal of description requiring pre-screening for GDF15 levels.	New data shows that up to CCI % of the study participants may have CCI GDF15 levels (above the current cut off); in addition, the removal of the GDF15 cut off level does not have any impact on participant safety.	Substantial
Section 10.8.6.1 (Fresh Tumour Biopsy)	Addition of text confirming that screening and on-treatment biopsies should be taken from the same lesion.	Clarification of sampling process for biopsies.	Non-substantial
Section 10.8.6.1.2 (Optional Fresh Paired Tumour Biopsies)	Updated to state that if CCI [redacted], every effort should be made to collect while on treatment.	Clarification regarding missed second biopsy and that for the CD8+ PET cohort, the first and second biopsy should be taken within CCI hours after the respective first and second CD8+ PET scans.	Non-substantial
Section 10.8.6.2 (Mandatory Archival Tumour Samples)	Updates made to the requirement of archival tumour tissue, number of slides/sections, and reference to laboratory manual for process, storage and shipment.	Clarification to confirm all the required details in one location.	Non-substantial
Appendix A3 (Informed Consent Process)	Text updated to confirm that separate Part B ICFs will be needed for sites in the CD8+ PET part of the study.	Clarification made to avoid confusion in terms of when a separate ICF is required for CD8+ PET part of study.	Non-substantial
Appendix E3 (Identification of	Deletion of process for central laboratory.	Hy's law assessments will be done locally and not via central laboratory.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Potential Hy's Law Cases)			
Appendix E8 (Laboratory Tests)	Table E8 header updated to "Local Laboratory Tests"	Hy's law assessments will be done locally and not via central laboratory.	Non-substantial
Appendix K (Protocol Amendment History)	Addition of this appendix.	Included as per template guidance.	Non-substantial
Throughout	Minor administrative changes.	Revisions made to correct errors in format, typography, or language.	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase I/IIa First-in-human, Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of AZD8853 in Participants with Selected Advanced/Metastatic Solid Tumours.

Short Title:

A First-in-human Study to Evaluate the Safety and Tolerability of AZD8853 in Participants with Selected Advanced/Metastatic Solid Tumours.

Rationale:

Chemotherapy and radiotherapy have historically been used for the treatment of patients with advanced/metastatic cancers; however, these strategies are usually not effective in controlling disease in the long term. Disease aggression is in part driven by the tumour immune microenvironment (TME) and in recent years there has been a focus on targeting different aspects of the TME to inhibit pro-tumourigenic immunosuppression and promote anti-tumour inflammatory responses. Therapeutics that target the programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint pathway have seen significant success in a number of solid tumour types by reversing cluster of differentiation (CD)8+ T cell exhaustion and driving a cytotoxic response. A caveat of this approach is that only a subset of participants will demonstrate long-term disease control, and so it is imperative to identify additional pathways for therapeutic development to promote anti-tumour immune response.

Growth differentiation factor 15 (GDF15), a transforming growth factor beta (TGF-β) superfamily cytokine, has been shown to affect the TME and is associated with a poor prognosis in a number of solid tumour types. CCI [redacted] As an antagonist to GDF15, the monoclonal antibody AZD8853 neutralizes the effects of GDF15 in preclinical tumour models. Effectively targeting GDF15 culminates in an enhanced cytotoxic anti-tumour immune response and reverses immunosuppression in the TME.

This study is primarily designed to evaluate the safety and tolerability of AZD8853. The study will include several "Substudies", the first of which will evaluate AZD8853 as monotherapy at increasing doses in participants with selected advanced/metastatic solid tumours who have elevated serum GDF15 levels and who have progressed or are refractory to at least one line of standard systemic therapy. This first Substudy will also characterise the pharmacokinetics

(PK) and immunogenicity of AZD8853 and explore potential biological activity by assessing pharmacodynamic (PD) biomarkers and anti-tumour activity. CCI [redacted]. The results from this study will guide future Substudies with AZD8853, which have yet to be defined.

AZD8853 is currently being developed as monotherapy but may be investigated in combination with other approved anti-cancer agents and/or investigational agents for greater efficacy in future Substudies, based upon emerging data. These combination Substudies may be added once a recommended Phase 2 dose (RP2D) for monotherapy has been defined based on emerging supportive preclinical and/or clinical data and scientific rationale in the first Substudy.

The overarching primary hypothesis for this study is that AZD8853 will demonstrate an acceptable safety, PK and PD profile, and evidence of preliminary efficacy in participants with selected advanced/metastatic solid tumours.

Key Objectives and Endpoints Applicable to all Substudies

The objectives and endpoints that are common for all Substudies are listed in Table 1. See the individual Substudies in the clinical study protocol for the objectives and endpoints specific to each of the Substudies.

Table 1 Objectives and Endpoints (All Substudies)

Type	Objectives	Endpoints
Primary		
Safety	To assess safety and tolerability, characterise DLTs (in dose escalation parts only) and determine the MTD or RP2D of AZD8853 in participants with selected advanced/metastatic solid tumours in each Substudy	• Incidence of AEs and SAEs • Incidence of DLTs in dose escalation parts only • Incidence of clinically significant changes from baseline in clinical laboratory parameters, vital signs, and ECG results • Incidence of AEs leading to discontinuation of AZD8853
Secondary		
Efficacy	To determine the preliminary anti-tumour activity of AZD8853 in participants with selected advanced/metastatic solid tumours in each Substudy	• According to RECIST v1.1: ORR, DCR at Week 15, DoR, and PFS • Change in target lesion tumour size from baseline • OS
Efficacy	To assess the efficacy of AZD8853 using longitudinal blood samples in participants with selected advanced/metastatic solid tumours in each Substudy	• Change in ctDNA from baseline levels between baseline and post-treatment timepoints
PK	To determine the PK of AZD8853 in serum when administered in participants with selected advanced/metastatic solid tumours in each Substudy	• PK parameters to be evaluated include but not limited to Cmax and AUC
Immunogenicity	To assess the immunogenicity of AZD8853 in participants with selected advanced/metastatic solid tumours in each Substudy	• Number and percentage of participants who develop detectable ADAs against AZD8853 in serum samples

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; AUC = area under the concentration-time curve; Cmax = maximum observed concentration; ctDNA = circulating tumour deoxyribonucleic acid; DCR = disease control rate; DLT = dose limiting toxicity; DoR = duration of response; ECG = electrocardiogram; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PD = pharmacodynamic(s); PFS = progression-free survival; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumours; RP2D = recommended Phase 2 dose; SAE = serious adverse event.

Overall Design

This study is a Phase I/IIa, multicentre, open-label study to evaluate the safety, PK, PD, and preliminary efficacy of AZD8853 in participants with selected advanced/metastatic solid tumours. Substudy 1 of the study will assess AZD8853 as a monotherapy. Additional Substudies may be added by substantial amendment evaluating AZD8853 in different combination cohorts.

Substudy 1

Substudy 1 will be a first time in human (FTiH), open-label, multicentre study, in which AZD8853 will be evaluated as monotherapy for safety, PK, PD, and preliminary efficacy in participants with selected advanced/metastatic solid tumours defined as:

- Second or later line setting of unresectable, locally advanced (Stage III) or metastatic (Stage IV) non-small-cell lung cancer (NSCLC) that have progressed on anti-PD-1/PD-L1 inhibitors with or without platinum-containing chemotherapy.
- Third or later line setting of Stage IV microsatellite stable-colorectal cancer (MSS-CRC) that have progressed on prior standard of care treatment.
- Second or later line setting of Stage IV urothelial carcinoma (UC) that have progressed on prior treatment with platinum and/or checkpoint inhibitors (CPI).

Substudy 1 will comprise 3 main parts (A, B and C), as shown in Table 2:

Table 2 Description of Study Parts

Study Part	Description	Number of Participants Planned
Part A (AZD8853) Dose Escalation		
Part A: Dose Escalation	• Dose escalation of AZD8853 in participants with selected advanced/metastatic solid tumours	• Up to 45 participants (assuming up to 5 dosing cohorts and 3-9 participants per cohort). • CCI [redacted].
Part B (AZD8853) PD/MoA Expansion		
Part B1 (Biopsy and CD8+ PET)	• PD cohort at alternative dose	• Up to approximately 20 participants (approximately 10 MSS-CRC and approximately 10 NSCLC participants). • Mandatory biopsies.
	• CD8+ PET	• Up to 10 participants (a subset of the 20 participants above).
Part B2 (Biopsy and CD8+ PET)	• PD cohort at MTD/HPDD	• Up to approximately 20 participants (approximately 10 MSS-CRC and approximately 10 NSCLC participants). • Mandatory biopsies.
	• CD8+ PET	• Up to 10 participants (a subset of the 20 participants above).

Study Part	Description	Number of Participants Planned
Part C (AZD8853) Efficacy Expansion*		
Part C1	• First indication at MTD/HPDD	Up to 40 participants. CCI [redacted].
Part C2	• Second indication at MTD/HPDD or • First indication at alternative dose	Up to 40 participants. CCI [redacted].

Abbreviations: CD8 = cluster of differentiation 8; HPDD = highest protocol-defined dose; MoA = mechanism of action; MTD = maximum tolerated dose; MSS-CRC = microsatellite stable-colorectal cancer; NSCLC = non-small-cell lung cancer; PD = pharmacodynamics; PET = positron emission tomography.
* If the RP2D cannot be adequately determined from Part B and additional data (eg, efficacy) is required to guide RP2D determination, then 2 dose levels in one indication will be investigated. If the RP2D is determined at the end of Part B, RP2D will be evaluated in 2 indications.

Disclosure Statement:

Substudy 1

This is a multi-part, open-label, dose escalation, PD/mechanism of action (MoA) expansion, and efficacy expansion Substudy.

Number of Participants:

Substudy 1

Across all parts of Substudy 1 up to a total of 165 eligible participants may be enrolled and treated with AZD8853, consisting of up to 45 participants in Part A, up to 40 participants in Part B and up to 80 participants in Part C.

Intervention Groups and Duration:

Refer to the relevant Substudy for details.

Safety Review Committee: Yes

A safety review committee (SRC) will be responsible for making dose escalation or dose de-escalation decisions and recommendations regarding further conduct of the study, during all phases of the study. The SRC will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data to monitor the ongoing safety profile of the study intervention.

Statistical Methods

Safety

Dose escalation will follow the modified toxicity probability interval (mTPI-2) algorithm and will be based on the dose limiting toxicity (DLT) evaluable population (all enrolled participants who complete the DLT evaluation period of 21 days after receiving at least 75% of the first infusion of study intervention, or who experience any DLT). Safety and tolerability will be assessed in terms of DLTs, adverse events (AEs), serious AEs (SAEs), vital signs,

clinical chemistry/haematology parameters, dose interruptions/discontinuations, and electrocardiogram (ECG) data. These variables will be collected for all participants. All safety analyses will be performed on the Safety Population (all participants who receive at least one dose of study intervention) and will be summarised using descriptive statistics. Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Efficacy

The efficacy endpoints for tumour response (objective response rate [ORR], disease control rate [DCR] at 15 weeks, duration of response [DoR], and percentage change in tumour size) will be summarised for the Response Evaluable Population (all dosed participants who have measurable disease at baseline) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 by Investigator assessment. The efficacy endpoints of progression-free survival (PFS) and overall survival (OS) will be summarised based on the Safety Population.

The RECIST tumour response data will be used to programmatically determine each participant's visit response and to derive the endpoints of ORR, DoR, DCR at 15 weeks, percentage change in tumour size, and PFS. Endpoints will be summarised using descriptive statistics and Kaplan Meier methods as appropriate.

Additionally, the percentage change in circulating tumour deoxyribonucleic acid (ctDNA) from pre-treatment (baseline) to each post baseline timepoint as well as the maximum change will be summarised using descriptive statistics on the Safety Population.

Pharmacokinetics

The PK analysis of the serum data for AZD8853 will be performed using the PK Population (all participants who receive at least one dose of study intervention with at least one reportable concentration). The actual sampling times will be used in the parameter calculations and the PK parameters will be derived using standard non-compartmental methods, if the data permits. It is anticipated that maximum concentration (Cmax), area under the curve (AUC), and other PK parameters will be calculated if the data allows.

Relevant descriptive statistics will be used to summarise PK parameters and concentrations.

Immunogenicity

Immunogenicity results will be analysed descriptively on the Immunogenicity Population (all participants who receive at least one dose of study intervention with at least one reportable immunogenicity measurement) by summarising the number and percentage of participants who develop detectable anti-drug antibodies (ADAs) against AZD8853 at protocol-specified timepoints. The immunogenicity titre may be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, efficacy, and safety may be

evaluated, if the data allow.

Depending on the extent of any impact, summaries of data relating to participants diagnosed with coronavirus disease 2019 (COVID-19), any impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatment, and other protocol deviations) may be generated.

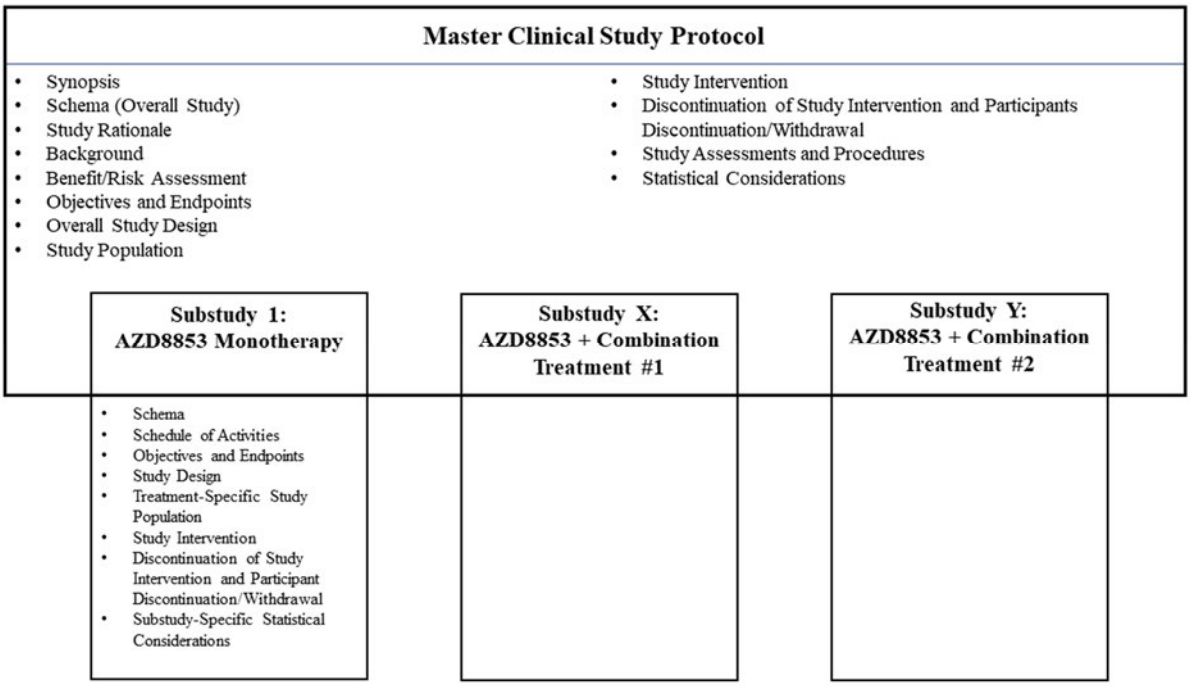
Further details of all analyses will be provided in a separate statistical analysis plan.

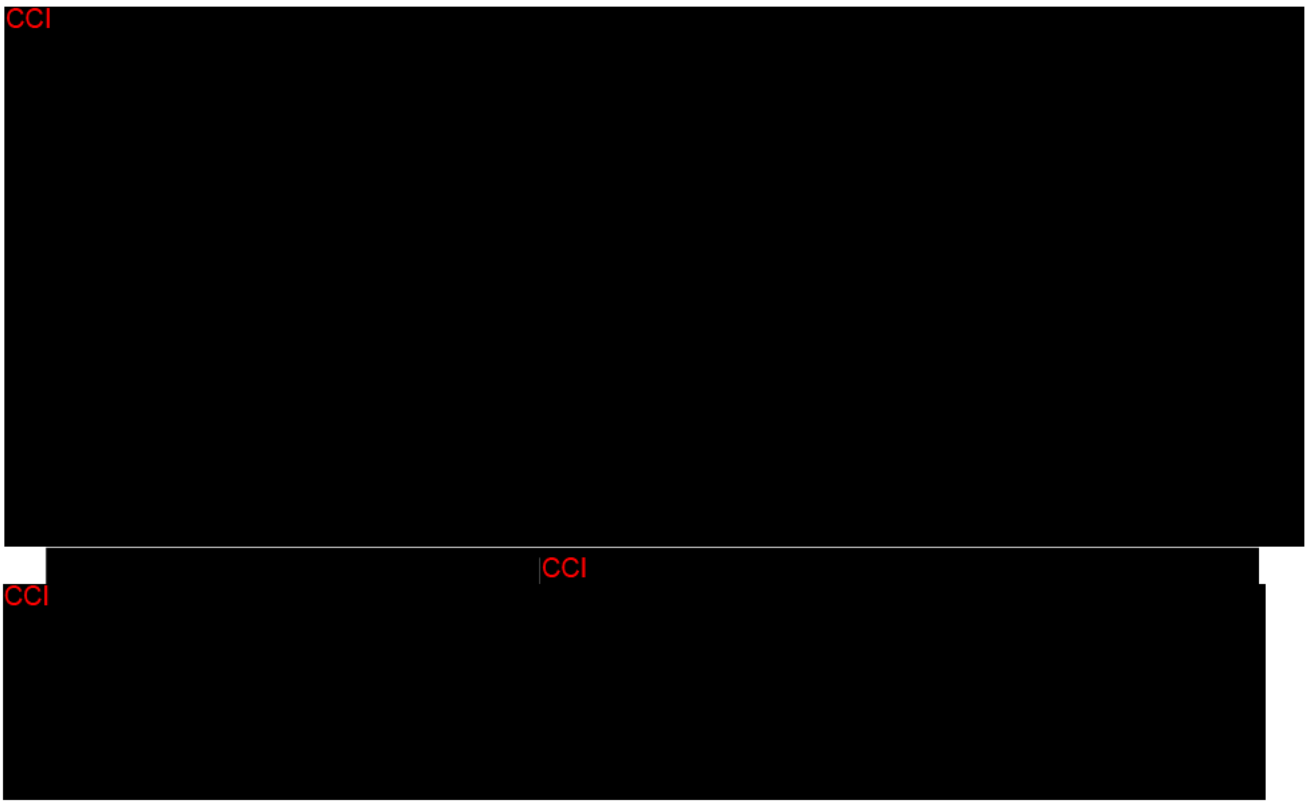
Interim analyses will be conducted separately for each Substudy and are described in the relevant Substudy.

1.2 Schema

Please see the individual schema for each study Substudy within the respective Clinical Study Protocol section.

Figure 1 AZD8853 Phase I/IIa Study in Selected Advanced/Metastatic Solid Tumours





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1.3 Schedule of Activities

Please see the individual schedule of activities for each study Substudy within the respective CSP section.

2 INTRODUCTION

AZD8853 is a humanized IgG1 mAb with an CCI [redacted]. AZD8853 specifically binds to and neutralizes GDF15, a TGF-β superfamily cytokine that is overexpressed in certain solid malignant tumours. GDF15 functions to regulate inflammation and has an immunosuppressive effect on T cells, DCs and myeloid-derived cell subsets. Neutralizing GDF15 leads to increased T cell proliferation and DC activation, thereby enhancing the immune response.

2.1 Study Rationale

Chemotherapy and radiotherapy have historically been used for the treatment of patients with advanced/metastatic cancers; however, these strategies are usually not effective in controlling disease in the long term. Disease aggression is in part driven by the TME and in recent years there has been a focus on targeting different aspects of the TME to inhibit pro-tumourigenic immunosuppression and promote anti-tumour inflammatory responses. Therapeutics that target the PD-1/PD-L1 immune checkpoint pathway have seen significant success in a number of solid tumour types by reversing CD8+ T cell exhaustion and driving a cytotoxic response. A caveat of this approach is that only a subset of participants will demonstrate long-term disease control, and so it is imperative to identify additional pathways for therapeutic development to promote anti-tumour immune response.

GDF15, a TGF-β superfamily cytokine, has been shown to affect the TME and is associated with a poor prognosis in a number of solid tumour types (Wischhusen et al, 2020; Liu et al, 2016; Mehta et al, 2014; Mehta et al, 2015; Traeger et al, 2019). High expression of GDF15 in the TME has been shown to lead to decreased DC activation, decreased cytotoxic CD8+ T cell infiltration and increased CD4+ Treg expansion (Wischhusen et al, 2020; Wang et al, 2021; Roth et al, 2010). As an antagonist to GDF15, the monoclonal antibody AZD8853 neutralizes the effects of GDF15 in preclinical tumour models. Effectively targeting GDF15 culminates in an enhanced cytotoxic anti-tumour immune response and reverses immunosuppression in the TME.

Substudy 1 of this study is primarily designed to evaluate the safety and tolerability of AZD8853 as monotherapy at increasing doses in participants with selected advanced/metastatic solid tumours who have elevated serum GDF15 levels and who have progressed or are refractory to at least one line of standard systemic therapy. Substudy 1 will also characterise the PK and immunogenicity of AZD8853 and explore potential biological activity by assessing PD biomarkers and anti-tumour activity. CCI [redacted]. The results from this Substudy will guide future clinical studies with AZD8853.

AZD8853 is currently being developed as monotherapy, but may be investigated in

combination with other anti-cancer agents or other types of agents for greater efficacy in the future. New Substudies for combination treatments may be added once monotherapy RP2D has been defined based on emerging supportive preclinical and/or clinical data and scientific rationale.

The overarching primary hypothesis for this study is that AZD8853 will demonstrate an acceptable safety, PK, and PD profile, and evidence of potential efficacy in participants with selected advanced/metastatic solid tumours.

2.2 Background

The TME plays an important role in tumourigenesis and overall disease aggression and thus has been targeted by many immune therapies. Patient prognosis is affected by both the extent of immune cell infiltration and how inflammatory or immune-suppressed these immune cells are (Tang et al, 2021; Waldman et al, 2020). To date, the most successful immunotherapies have focused on modulating cytotoxic T cell responses. However, tumour progression is controlled by several immune cell types and soluble factors that can be released by both tumour and non-tumour cells and research endeavours have sought to identify novel therapeutics that can target multiple aspects of the TME.

GDF15 has been linked to the development of cancers (Wischhusen et al, 2020; Bauskin et al, 2006). High levels of GDF15 alter the TME toward an immunosuppressive, tumour-"promoting" microenvironment. CCI [redacted] (unpublished AstraZeneca clinical trial analyses). CCI [redacted]
Preclinical in vivo research has shown that anti-GDF15 treatment causes infiltration of T cells and activation of DCs, leading to an anti-tumour response in anti-PD-L1 resistant models. This suggests that anti-GDF15 may provide an alternative therapy for patients whose tumours have previously failed to respond to anti-PD-L1 therapy. Since anti-GDF15 is hypothesised to have the dual effect of recruiting T cells to the TME and alleviating immune suppression, this novel therapeutic is expected to remodel the TME and, therefore, improve the anti-tumour immune response in patients who have a TME that is either poorly infiltrated with T cells or highly immunosuppressive.

2.2.1 Tumour Type Selection

In cancer, elevated serum GDF15 levels have been reported in many solid malignancies, including colon (Mehta et al, 2015), lung (Liu et al, 2016) and bladder cancer (Traeger et al, 2019). According to unpublished work conducted by AstraZeneca with CCI [redacted]

[redacted] Similarly, higher levels of GDF15 were found in NSCLC samples, where high serum levels correlated with fewer cytotoxic CD8+ T cells and reduced DC gene expression signatures. Lastly, the correlation was also found in bladder cancer samples, where high GDF15 levels correlated with low CD8+ T cell numbers (IHC) and low cytotoxic activity and NK cell gene expression signatures. Furthermore, emerging data from ongoing clinical trials conducted by AstraZeneca suggest that [redacted]% of pre-treated patients in these indications have elevated GDF15 levels (>[redacted] pg/mL). Lastly, in all of these tumour types elevated GDF15 levels have been correlated with poor outcomes (Mehta et al, 2015; Liu et al, 2016; Traeger et al, 2019).

2.3 Benefit/Risk Assessment

Detailed information about the known and anticipated benefits and potential risks of AZD8853 are found in the IB.

2.3.1 Risk Assessment

This is the FTiH trial for AZD8853; no clinical data are available and there are no identified risks at this time. The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP requirements, and applicable regulatory requirements.

Preclinical Work

The initial single dose (intravenous) PK and PD non-GLP study was performed in male cynomolgus monkeys where animals were dosed [redacted] mg/kg, [redacted] mg/kg, or [redacted] mg/kg followed by a 4-week recovery period. Single doses were well tolerated with no adverse clinical reactions or clinical pathology observed; specifically, there were no changes to coagulation, complement, or immune subsets.

A 3-month GLP toxicology study was performed in cynomolgus monkeys with an 8-week recovery period. Both male and female monkeys were dosed [redacted] mg/kg, [redacted] mg/kg, or [redacted] mg/kg AZD8853 by weekly intravenous (15 min) infusion for 14 administrations. There were no AZD8853-related changes in body weight, or neurological, ECG, respiratory or BP examinations. There were no changes in clinical pathology (haematology, clinical chemistry, urinalysis or cytokine analysis), nor immunophenotyping. No AZD8853-related organ weight changes were noted. Minimal to slight vascular/perivascular inflammatory changes were noted in the kidney, heart, and gall bladder of an individual animal administered the [redacted] dose of [redacted] mg/kg which is suggestive of secondary immune complex formation related vascular injury. There were no histopathological changes observed in the remaining 5 animals at the [redacted] dose of [redacted] mg/kg or the [redacted] dose of [redacted] mg/kg, respectively. Refer to the IB for detailed information about the GLP toxicology studies.

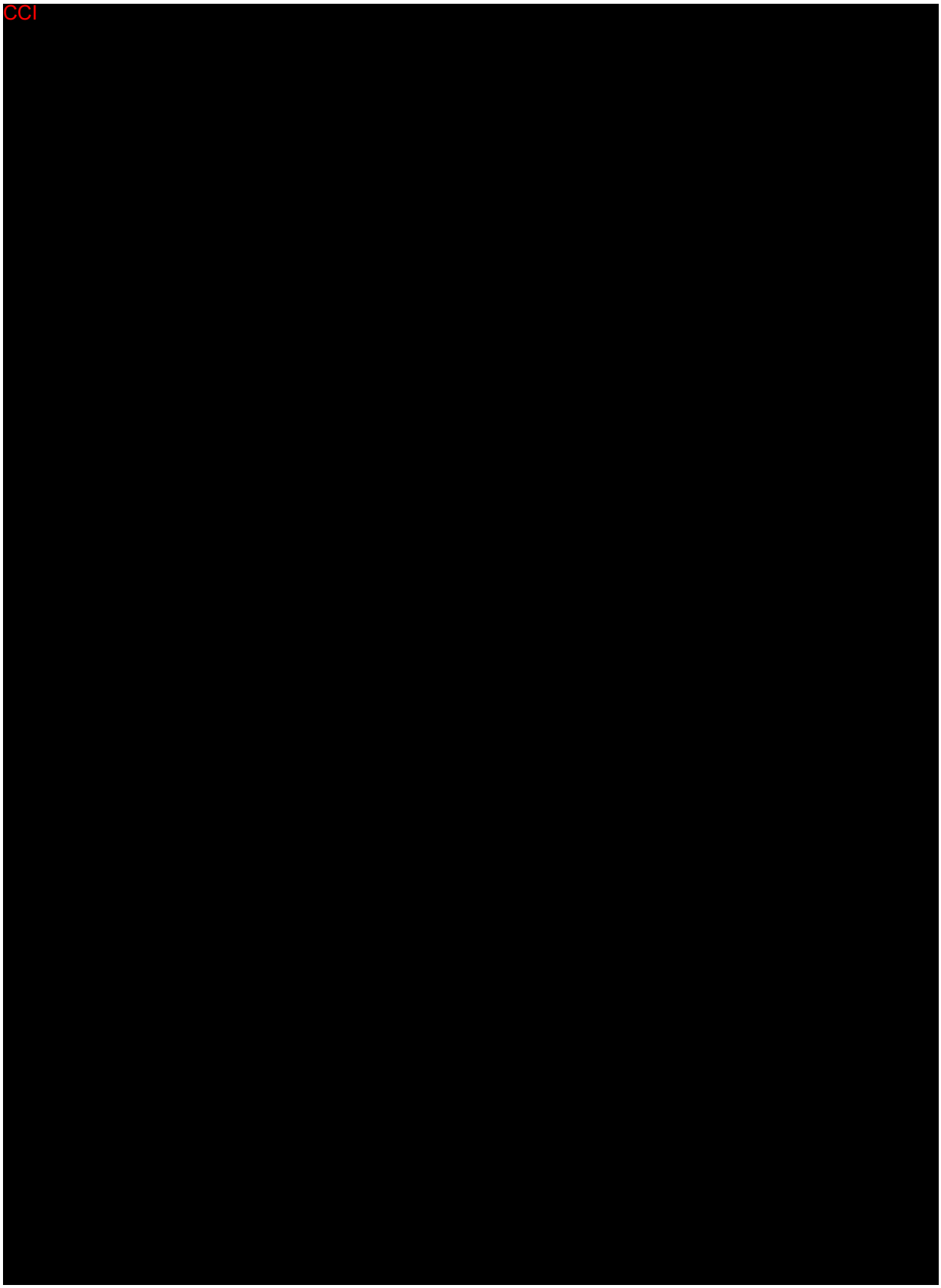
Potential Risks

Based upon the GLP toxicology studies to date, there are no identified risks for AZD8853.

The potential risks for AZD8853 include [redacted]. These risks are based on animal data, including [redacted] mice models, described in the literature. Immune complex disease is a potential risk based on preclinical findings in the GLP toxicology study. Additional potential risks include [redacted], which can occur after infusions with mAbs. The TMG are provided as a separate document. The risk assessment for AZD8853 is provided in Table 3.

[redacted]

CCI



CCI

[redacted]

2.3.2 Benefit Assessment

In nonclinical pharmacology studies, AZD8853 was able to CCI [redacted]. In addition, AZD8853 was able to CCI [redacted] Overall, the preclinical data from both in vitro and in vivo models suggest that AZD8853 has the potential

to induce clinical response in participants with selected advanced/metastatic cancers.

2.3.3 Overall Benefit/Risk Conclusion

There remains an unmet need for improved therapies for patients with advanced/metastatic solid tumours. The design of this current study aims to minimize potential risks to participants based on the inclusion and exclusion criteria, restrictions on concomitant medication during the study, continuous safety monitoring (including review of all available safety, PK, and other relevant data by the SRC), and TMGs. The potential risks are designated AESIs and hence are subject to intensive safety monitoring. Thus, the benefit/risk assessment for this Phase I/IIa study appears acceptable based upon the poor outcomes for this patient population and the strength of the scientific hypothesis under evaluation.

More detailed information about the known and anticipated benefits and potential risks of AZD8853 may be found in the IB.

2.3.4 Benefit/Risk Pertaining to Study Conduct During the COVID-19 Pandemic

Cancer patients have an increased risk of exposure to SARS-CoV-2 due to frequent hospital or clinic visits for treatment and monitoring. A retrospective cohort study of 28 COVID-19-infected cancer participants from 3 hospitals in Wuhan, China, reported that a CCI of participants CCI %; N = CCI) were suspected to have acquired the infection by hospital-associated transmission (Yu et al, 2020; Zhang et al, 2020). Participants with cancer may have a higher risk of a poorer outcome if infected with SARS-CoV-2 than individuals without cancer but current evidence appears insufficient to support a conclusive association between cancer in general and COVID-19 (Xia et al, 2020).

This study will enrol participants with selected advanced/metastatic solid tumours. Participants in this study will receive AZD8853 treatment that leads to inhibition of GDF15 as part of the treatment strategy. Overall, the intervention received and procedures during the course of this study are considered to have low risk for increasing susceptibility to SARS-CoV-2 infection.

Furthermore, at this stage of disease, participants would typically have frequent healthcare-related visits, irrespective of participation in a clinical study. Therefore, it is anticipated that participation in this clinical study should not significantly increase a participant's risk of exposure to COVID-19.

Novel treatment options are needed to improve the long-term prognosis for participants with advanced/metastatic solid cancer tumours, which are associated with chemoresistance, extremely poor prognosis, and a high risk of developing cancer-related death. AZD8853 could be a potential treatment option in this patient population with high unmet medical need. The

scheduled safety assessment visits that are considered in excess of standard-of-care are intended to monitor the participants involved in the study. Thus, although there may be increased risk to participants by exposure to COVID-19 during study visits, this is offset by the benefit of participating in a clinical trial.

In accordance with EMA and FDA guidelines (EMA-CTFG-EC, 2021; FDA 2021), a risk assessment will be conducted in collaboration with Investigators for each site and participant prior to site initiation/participant enrolment and on an ongoing basis throughout the study to assess whether additional measures may be necessary to ensure participant safety and data validity. Measures may include postponement of study start on a global, country, or site level or suspension of recruitment of participants in locations with an increased risk of COVID-19 related disruption.

If there is a need to reconsent study participants for the implementation of new urgent changes in study conduct, additional guidance on alternative means of obtaining reconsent to avoid unnecessary study visits is provided in Appendix A. Any deviations to the CSP necessary to safeguard participant safety or data validity as a result of COVID-19-related disruption will be recorded and any permanent changes requiring an amendment to the CSP will be communicated to regulatory authorities and IRBs/IECs in line with relevant local guidance and procedures.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Please see the study-specific objectives and endpoints for each Substudy within the respective Substudy section. The following objectives are applicable for all Substudies.

Type	Objectives	Endpoints
Primary		
Safety	To assess safety and tolerability, characterise DLTs (in dose escalation parts only) and determine the MTD or RP2D of AZD8853 in participants with selected advanced/metastatic solid tumours in each Substudy	• Incidence of AEs and SAEs • Incidence of DLTs in dose escalation parts only • Incidence of clinically significant changes from baseline in clinical laboratory parameters, vital signs, and ECG results • Incidence of AEs leading to discontinuation of AZD8853
Secondary		
Efficacy	To determine the preliminary anti-tumour activity of AZD8853 in participants with selected advanced/metastatic solid tumours in each Substudy	• According to RECIST v1.1 ORR, DCR at Week 15, DoR, and PFS • Change in target lesion tumour size from baseline • OS
Efficacy	To assess the efficacy of AZD8853 using longitudinal blood samples in participants with selected advanced/metastatic solid tumours in each Substudy	• Change in ctDNA from baseline levels between baseline and post-treatment timepoints
PK	To determine the PK of AZD8853 in serum when administered in participants with selected advanced/metastatic solid tumours in each Substudy	• PK parameters to be evaluated include but not limited to Cmax and AUC
Immunogenicity	To assess the immunogenicity of AZD8853 in participants with selected advanced/metastatic solid tumours in each Substudy	• Number and percentage of participants who develop detectable ADAs against AZD8853 in serum samples

Abbreviations: ADA = antidrug antibodies; AE = adverse event; AUC = area under the concentration time curve; Cmax = maximum observed concentration; ctDNA = circulating tumour deoxyribonucleic acid; DCR = disease control rate; DLT = dose limiting toxicity; DoR = duration of response; ECG = electrocardiogram; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PD = pharmacodynamic(s); PFS = progression free survival; PK = pharmacokinetic(s); RECIST = response evaluation criteria in solid tumours; RP2D = recommended Phase 2 dose; SAE = serious adverse event.

4 STUDY DESIGN

4.1 Overall Design

4.1.1 Master Protocol Structure

The overall study design will include a Master Protocol with Substudies. Information relating to the overall study, including study objectives, rationale, master inclusion and exclusion criteria, safety assessments, and AE reporting can be found in the Master Protocol (ie, Sections 1-9). In addition to the Master Protocol, individual "Substudies" will contain elements specific to each individual Substudy. Substudy 1 as described below, includes both a dose escalation and 2 expansions for monotherapy. The content of additional Substudies has not yet been defined and will be further added based on emerging supportive preclinical data.

The information in this Master Protocol cannot be superseded by information in the Substudies. Any change to the study master elements (ie, this Master Protocol) or Substudies will be submitted to Regulatory Authorities and ethics committees according to the local legislation/requirements.

Study drug-specific information including doses and justifications, toxicity management, dose modifications and concomitant medications can be found in the relevant Substudy(ies).

4.1.2 Substudy Naming Conventions

Initially, the study will consist of one Substudy (Substudy 1) evaluating the safety, PK, PD, and preliminary efficacy of AZD8853 as monotherapy in participants with selected advanced/metastatic solid tumours. Additional Substudies may be added by substantial amendment evaluating AZD8853 in different combination cohorts. These different combination cohorts will be determined by emerging preclinical data using combinations of approved therapies and/or investigational agents which have established safety data in humans.

Table 5 Substudy Naming Conventions

Substudy	Tumour Type	Intervention
Substudy 1 – Monotherapy Escalation and Expansion	NSCLC MSS-CRC UC	AZD8853
Potential combination therapy Substudies [a]		
Substudy X – AZD8853 + [combination treatment #1]	TBD	AZD8853 + [combination treatment #1]
Substudy Y – AZD8853 + [combination treatment #2]	TBD	AZD8853 + [combination treatment #2]

[a] Anticipated combination cohort Substudies will be numbered per the order added to the study protocol (Substudy 2, Substudy 3, etc).

Abbreviations: MSS-CRC = microsatellite stable-colorectal cancer; NSCLC = non-small-cell lung cancer; TBD = to be decided; UC = urothelial carcinoma.

4.1.3 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note, in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed for previously screened participants. The Investigator should confirm this with the designated study physician.
- Home or remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix G.

4.2 Scientific Rationale for Study Design

This is a FTiH study primarily designed to evaluate the safety and tolerability of AZD8853 at increasing doses in participants with selected metastatic/advanced solid tumour and for whom no standard-of-care exists. The study will also characterise the PK of AZD8853 and explore potential biological activity by assessing PD and CCI and anti-tumour activity. The results from this study will form the basis for decisions for future studies. The ability to acquire appropriate consent to collect biological samples is of utmost importance in

order to establish an archive and allow future meta-analysis of data derived from a number of studies with AZD8853.

The Master Protocol with Substudy structure allows for the optimization of both dose and schedule of AZD8853 as monotherapy and in combination with anti-cancer agents, including intensive safety monitoring followed by expansion cohorts in specific indications. In addition, the Master Protocol with Substudy structure allows flexibility to open and close different AZD8853 combinations at a different pace based on emerging data. This allows for a more fluid development of AZD8853 in combinations and indications with the greatest potential to benefit participants.

Key aspects of the study, such as starting dose of AZD8853 in Substudy 1, the dose escalation, stopping criteria, cohort sizes, and study endpoints are based upon accepted methodology for Phase I/II oncology studies.

4.3 Justification for Dose

Information on dose justification is provided in the respective Substudies.

4.4 End of Study Definition

The end of the study is defined as 18 months after the last enrolled participant received his/her last dose of study intervention or when the Sponsor stops the study, whichever occurs first.

4.4.1 Study Stopping Criteria

AstraZeneca reserves the right to temporarily suspend or permanently terminate this study or components of the study at any time. The reasons for temporarily suspending or permanently terminating the study may include, but are not limited to the following:

- Fatal event deemed related to study therapy (probable or certain causality after full etiological work-up). This will also result in a comprehensive review of safety.
- Unexpected and life-threatening events deemed related to study therapy.
- Sponsor decision that the study participants are placed at undue safety risk.
- Participant enrolment is unsatisfactory.
- Noncompliance that might significantly jeopardize the validity or integrity of the study.
- Sponsor decision to terminate development of the study intervention.

If AstraZeneca determines that temporary suspension or permanent termination of the study or components of the study is required, AstraZeneca will discuss the reasons for taking such action with all participating Investigators. When feasible, AstraZeneca will provide advance notice to all participating Investigators of the impending action.

If the study or components of the study are suspended or terminated for safety reasons, AstraZeneca will promptly inform all Investigators and/or institutions conducting the study. AstraZeneca will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study or components of the study is suspended for safety reasons and it is deemed appropriate by AstraZeneca to resume the study or components of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

5 STUDY POPULATION

All criteria and considerations listed in this section are for the master study design and apply to all Substudies of the study. Additional Substudy-specific criteria and considerations are listed in the study population section of the relevant Substudy.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

The below are the master inclusion criteria for all Substudies of the study; all participants must meet the criteria described in the relevant Substudy in addition to those described below. Where Substudy-specific criteria are more stringent than master study criteria, the Substudy-specific criteria take precedent.

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Provision of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, and analyses.
3. Provision of signed and dated written CCI Information informed consent prior to collection of samples for CCI that supports the CCI .

Age

4. Participant must be at least 18 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

5. Have a life expectancy of ≥ 12 weeks.
6. Participants must have at least one lesion, that qualifies as a RECIST v1.1 TL at baseline. Tumour assessment by CT scan or MRI must be performed within 28 days prior to treatment.
   a) A previously irradiated lesion can be considered a TL if the lesion is well defined, measurable per RECIST v1.1, and has clearly progressed during or after most recent therapy.
   b) Participants undergoing paired tumour biopsies must have additional NTLs that can be biopsied at acceptable risk as judged by the Investigator or if no other lesion is

deemed suitable for biopsy, then a RECIST v1.1 TL used for biopsy must be ≥ 2 cm in longest diameter (Please see requirements outlined in Appendix F).

7. ECOG performance status of 0 to 1 with no deterioration over the previous 2 weeks.
8. Adequate organ and bone marrow function measured within 14 days prior to first dose as defined in Table 6.
   Note that one rescreen is permitted for participants if required, in line with Section 5.4.

Table 6 Criteria for Adequate Organ and Marrow Function

Parameter		Value
Haematological	Haemoglobin	≥ 9.0 g/dL (5.59 mmol/L) with no blood transfusions (packed red blood cells) in the past 28 days.
	Absolute neutrophil count	≥ 1.5 × 10^9/L (1,500 per mm^3)
	Platelet count	≥ 100 × 10^9/L (100,000 per mm^3) with no platelet transfusions in the past 10 days.
Hepatic	Total bilirubin	≤ 1.5 × ULN in the absence of Gilbert's syndrome
		≤ 3 × ULN if the participant has Gilbert's syndrome
	Alanine transaminase and aspartate transaminase	≤ 3.0 × ULN. ≤ 5 × ULN in case of liver metastasis.
Renal	Calculated creatinine clearance [a]	≥ 50 mL/minute[2] (≥ 45 mL/minute[2] for urothelial carcinoma participants).

[a] As determined by Cockcroft-Gault (using actual body weight):

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{Serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{Serum creatinine (mg/dL)}}$$

Abbreviations: ULN = upper limit of normal.

5.2 Exclusion Criteria

The below are the master exclusion criteria for all Substudies of the study; all participants must meet the criteria described in the relevant Substudy in addition to those described below. Where Substudy-specific criteria are more stringent than master study criteria, the Substudy-specific criteria take precedent.

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participants with a history of thromboembolic events within 6 months of Cycle 1 Day 1 unless they received adequate treatment. Please discuss with the Study Physician to determine study eligibility.

2. Unresolved toxicities of ≥ Grade 2 (CTCAE v5.0) from prior therapy (excluding vitiligo, alopecia, endocrine disorders that are controlled with replacement hormone therapy, asymptomatic laboratory abnormalities). Participants with ≥ Grade 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
3. Symptomatic CNS metastasis or leptomeningeal disease.
4. Ongoing or an active infection, including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBsAg result), hepatitis C, or HIV (positive HIV 1/2 antibodies).
5. Participants with a past or resolved HBV infection (defined as the presence of anti-HBc and absence of HBsAg) are eligible. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
6. Uncontrolled intercurrent illness, including but not limited to, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the participant to give written informed consent.
7. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
   (a) Participants with vitiligo or alopecia.
   (b) Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
   (c) Any chronic skin condition that does not require systemic therapy.
   (d) Participants without active disease in the last 5 years may be included but only after consultation with the Study Physician.
   (e) Participants with celiac disease controlled by diet alone.
8. Other invasive malignancy within 2 years except for non-invasive malignancies.
9. Known allergy or hypersensitivity to IMP formulations, imaging agents (per Investigator's discretion; if the participant can receive steroids and is stable prior to imaging), or any of the study intervention excipients.
10. Body weight loss > 10% within 30 days of screening visit.
11. Type 2 diabetes managed by metformin (please refer to Table 8).

Prior/Concomitant Therapy

12. Current or prior use of immunosuppressive medication within 14 days before the first dose of study intervention is excluded. The following are exceptions to this criterion:
    a) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intraarticular injection).
    b) Systemic corticosteroids at physiological doses not to exceed 10 mg/day of prednisone or its equivalent or 2 mg/day of dexamethasone or equivalent for participants with CNS metastases. Participants with brain metastases unless treated, asymptomatic, stable, and not requiring continuous corticosteroids at a dose of > 10 mg prednisone/day or equivalent for at least 4 weeks prior to start of study.
    c) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
13. Prior therapy targeting GDF15 or GRFAL.
14. Any concurrent chemotherapy, IMP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

Prior/Concurrent Clinical Study Experience

15. Enrolment into another interventional clinical trial where:
    a) Study intervention was administered within 28 days, or 5 half-lives of the previous intervention, whichever is shorter, prior to the first dose of AZD8853.
    b) Concurrent enrolment in another clinical study unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

Other Exclusions

16. History of organ transplant.
17. Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Participants, if enrolled, should not receive live vaccine while receiving study intervention and up to 30 days after the last dose of study intervention.
18. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study intervention or anticipation of the need for major surgical procedure during the course of the study. Note: Local surgery of isolated lesions for palliative intent is acceptable.
19. Mean QTcF $\geq$ 470 ms calculated from 3 ECGs (within 5 minutes).
20. COVID-19:
    a) Negative COVID-19 test is required for participants who have clinical signs and symptoms consistent with COVID-19 (eg, fever, dry cough, dyspnoea, sore throat,

fatigue, loss of sense of smell or taste). If the participant tests positive for COVID-19, a subsequent negative test result and symptom resolution are required before Cycle 1 Day 1.

b) COVID-19 vaccination should not be given for 72 hours prior to administration of the first dose of AZD8853 or during the DLT period.

21. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
22. Female participants who are pregnant or breastfeeding, or male or female participants of reproductive potential who are not willing to employ effective birth control from screening to 3 months after the last dose of AZD8853 (Section 5.3).
23. Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

5.3 Lifestyle Considerations

5.3.1 Contraception

The following restrictions apply while the participant is receiving study treatment and for the specified times before and after:

- Female participants of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (see Table 7) from the time of screening and must agree to continue using such precautions for 3 months after the last dose of AZD8853. Male partners of a female participant must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Female participants should refrain from breastfeeding throughout this period. In addition, female participants must refrain from egg donation while on study and for 3 months after the final dose of AZD8853.
- Non-sterilized male participants who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 3 months after the last dose of study drug. Male participants should refrain from sperm donation for 3 months after the last dose of AZD8853. Female partners of a male participant must use a highly effective method of contraception throughout this period.
- Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as 12 months with no menses without an alternative medical cause).
- Acceptable non-hormonal birth control methods include:

  a) Total/True abstinence: When the participant refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must

continue for the total duration of the study and for at least 3 months after the last dose of study drug. Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a study) and withdrawal are not acceptable methods of contraception.

b) Vasectomized sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.

c) Tubal occlusion PLUS male condom.

d) Intrauterine device PLUS male condom. Coils must be copper-banded.

e) Highly effective methods of contraception are described in Table 7. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 7 Highly Effective Methods of Contraception (< 1% Failure Rate)

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®). • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®). • Injection: Medroxyprogesterone injection (eg, Depo-Provera®). • Combined Pill: Normal and low dose combined oral contraceptive pill. • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®). • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill.

[a] This is also considered a hormonal method.

5.3.2 Activity

Participants will abstain from strenuous exercise for 48 hours before each GDF15 blood collection timepoint. Participants may participate in light recreational activities during the study (eg, watching television, reading) (Kleinert et al, 2018; Campderrós et al, 2020).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study and do not receive study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any SAE and medications administered for a given SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Each participant may undergo only one rescreen in the study. Rescreened participants should be assigned the same participant number as for the initial screening. Rescreening should be documented so that its effect on study results, if any, can be assessed. Individuals who fail screening should have the reason recorded in the eCRF to indicate them as screen failures.

6 STUDY INTERVENTION

Study intervention is defined as any IMP(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilised by a study participant according to the study protocol. Additional details can be found in the Handling Instructions.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Medicinal Product – AZD8853

Intervention name	AZD8853
Type	Biologic
Dose formulation	Concentrate for solution for infusion CCI mg/mL AZD8853 in CCI mM CCI, CCI mM CCI, CCI % (w/v) CCI, pH CCI
Unit dose strength	CCI mg/vial (CCI mg/mL)
Minimum dosage level Maximum dosage level	300 mg 3000 mg
Route of administration	i.v. infusion
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and labelling	Study intervention will be provided in vials in a carton. Each vial and carton will be labelled in accordance with country regulatory requirements.

Abbreviations: IMP = investigational medicinal product; i.v. = intravenous; NIMP = non-investigational medicinal product.

6.1.1.1 Identity of Investigational Medicinal Product

The IMP kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial are labelled with the same unique sequence number range.

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention.

3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.
4. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.2.1 Investigational Medicinal Product Inspection

Each vial selected for dose preparation should be inspected.

AZD8853 will be supplied by AstraZeneca as a [redacted] and administered via i.v. infusion.

If any defects are noted with the IMP(s), the Investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 6.2.5) for further instructions.

6.2.2 AZD8853 Preparation and Administration

The dose of AZD8853 for administration must be prepared by the Investigator's or site's designated IMP manager using aseptic technique.

Total time from needle puncture of the AZD8853 vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours. No incompatibilities between AZD8853 and polyolefin i.v. bags have been observed for i.v. administration.

Doses of AZD8853 will be administered using an i.v. bag containing [redacted], with a final AZD8853 concentration ranging from [redacted] mg/mL and delivered through an i.v. administration set with a [redacted]-µm filter. Add required volume of AZD8853 for dose level (using calculation below) to the i.v. bag.

The volume of AZD8853 (in mL) to add to the i.v. bag is calculated as follows:

$$Drug\ Product\ Volume\ (mL) = \frac{dose\ level\ (mg)}{50\ mg/mL}$$

where 50 mg/mL is the nominal AZD8853 drug product concentration.

The i.v. bag size should be ≤CCI mL and be selected such that the final concentration is within CCI mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time for AZD8853 is 1 hour; however, if there are interruptions during infusion, the total allowed infusion time should not exceed 4 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

Flush the i.v. line with a volume of i.v. diluent equal to the priming volume of the infusion set used after the contents of the i.v. bag are fully administered or complete the infusion according to institutional policy to ensure the full dose is administered.

If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. AZD8853 does not contain preservatives, and any unused portion must be discarded.

6.2.3 Treatment Administration

No premedication for the prevention of IRRs prior to the first infusion of AZD8853 is permitted (ie, primary prophylaxis). Any planned premedication with acetaminophen (paracetamol), histamine (H1 and H2)-receptor antagonists, with subsequent infusions of AZD8853 following an IRR (ie, secondary prophylaxis) is permitted. Steroids should not be used as routine premedication for Grade 1 or 2 IRRs. If more than one participant during the course of the study develops a Grade ≥ 3 IRR during the first infusion, the SRC may recommend premedication for all subsequent participants to be implemented for the first infusion as follows: paracetamol/acetaminophen (500 to 1000 mg orally) and diphenhydramine (25 to 50 mg orally or i.v.; or an alternative antihistamine at an adequate dose), should be administered approximately 30 minutes prior to infusion with AZD8853. For additional premedication guidelines for the prevention of IRR, refer to Section 6.5.

6.2.4 Monitoring of Dose Administration

Participants will be monitored during and after infusion of AZD8853. Vital signs will be measured according to the schedules described in Section 8.2.3. In the event of an IRR, or any other AE, see TMGs for toxicity management and dose modification.

As with any biological product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

The Investigator's or site's designated IMP manager is required to maintain accurate IMP accountability records. Upon completion of the study, copies of IMP accountability records will be returned to AstraZeneca. All unused IMPs will be returned to an AstraZeneca authorized depot or disposed of upon authorization by AstraZeneca according to the investigational site policy.

6.2.5 Reporting Product Complaints

Any defects with the IMP must be reported *immediately* to the Sponsor Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to the Sponsor and investigated further with the Product Complaint Department. During the investigation of the product complaint, all IMP must be stored at labelled conditions unless otherwise instructed.

Contact information for reporting product complaints:

Email: productcomplaints@astrazeneca.com

Phone: +1-301-398-2105

Mail: AstraZeneca
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

6.2.6 Additional Study Drugs

Provided in respective Substudy.

6.2.7 Labelling

Labels for the IMP will be prepared in accordance with good manufacturing practice and local regulatory guidelines. Label text will be translated into local languages, as required.

6.2.8 Storage

AZD8853 vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. All IMPs should be kept in a secure and dry place. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

6.2.9 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance. Details of treatment with IMPs for each participant will be recorded in the eCRF.

6.2.10 Accountability

The Investigator's or site's designated IMP manager is required to maintain accurate IMP accountability records. Upon completion of the study, copies of IMP accountability records will be returned to the Sponsor. All unused IMP will be returned to a Sponsor-authorized depot or disposed of upon authorization by the Sponsor.

6.3 Measures to Minimise Bias: Randomization and Blinding

This is an open-label study; no blinding is required. Each potential participant is assigned a unique participant identification number at the screening visit after signing consent. Once a participant is assigned a unique identification number, it cannot be reused for another participant. Study intervention will be dispensed at the study visits summarised in the relevant Substudy. Returned study intervention should not be re-dispensed to the participants.

If an unscheduled assessment is performed, and the participant has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed to minimise any unintentional bias caused by some participants being assessed at a different frequency than other participants.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

A record of the volume of AZD8853 infusion administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

Deviations from the prescribed dosage regimen should be recorded in the eCRF. The

Investigational Product Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention.

6.5 Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including route of administration, dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must be instructed not to take any medications, including OTC products, herbal or natural remedies, vitamins and supplements, without first consulting with the Investigator.

Authorised/approved COVID-19 vaccines can be given to participants enrolled in this study as long as these do not represent a prohibited concomitant medication. Investigators should follow the CSP, their local prescribing information, and policies when considering if vaccination against COVID-19 is appropriate for their participants enrolled in an AstraZeneca clinical study. COVID-19 vaccination should not be given for 72 hours prior to administration of the first dose of AZD8853 or during the DLT period.

For any authorised/approved COVID-19 vaccine, specific considerations should be given to the relevant labelling information (ie, “Indications,” “Contraindications,” “Warnings and Precautions,” “Adverse Reactions”) on its use in this study. In any case, COVID-19 vaccination details must be captured in the eCRF as concomitant medication, and adverse reactions reported.

Prohibited concomitant therapies are listed in Table 8 and permitted concomitant therapies are listed in Table 9. Concomitant medication additional to those listed in Table 8 may be considered on a case-by-case basis by the Investigator in consultation with the Study Physician if required.

Table 8 Prohibited Concomitant Medications

Prohibited Medication/Class of Drug	Usage
Any investigational therapy including anti-cancer therapy other than those under investigation in this study	Should not be given concomitantly while the participants are on study intervention
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the participants are on study intervention
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the participants are on study intervention, unless specified in a Substudy. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions for palliative intent may be acceptable [eg, by local surgery or radiotherapy]) upon consultation with study physician.
Live attenuated vaccines	Should not be given through 30 days after the last dose of study intervention
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the immunotherapy infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study intervention-related AEs • Short-term premedication for participants receiving combination agent where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in participants with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the participant (eg, chronic obstructive pulmonary disease, radiation, nausea, etc)
Metformin	Metformin has been shown to induce GDF15 gene expression, thereby elevating circulating GDF15 levels significantly. One study showed that a one-time dose of metformin increased mean circulating GDF15 levels about 2.5-fold **(Coll et al, 2020)**. To prevent falsely high GDF15 level results, participants must not take metformin for at least 72 hours prior to the screening GDF15 blood sample and should be switched to an acceptable alternative; the participant must demonstrate controlled diabetes mellitus on this

Table 8 Prohibited Concomitant Medications

Prohibited Medication/Class of Drug	Usage
	alternative at least 7 days prior to starting the study intervention on Cycle 1 Day 1.
Herbal and natural remedies	Should not be given concomitantly unless agreed by the Sponsor

Abbreviations: AE = adverse event; CTLA-4 = cytotoxic T-lymphocyte associated antigen; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1.

Table 9 Permitted Concomitant Medications

Supportive Medication/Class of Drug	Usage
Premedication for management of diarrhoea, nausea, and vomiting	Permitted after but not before the first dose of study intervention
Blood transfusions	Permitted at any time during the study
Erythropoietin	Prophylactic erythropoietin should not be started during Cycle 1 of the study but may be started during Cycle 2 and after. Participants already receiving erythropoietin at the time of screening may continue it provided they have been receiving it for more than one month at the time study treatment has started.
G-CSF	G-CSF should not be used prophylactically during Cycle 1, but may be considered after Cycle 1
Megestrol acetate	Permitted for appetite stimulation
Bisphosphonates, and denosumab	Permitted for treatment of bone metastases
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed in Table 8	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all participants
Inactivated viruses, such as those in the influenza vaccine, and COVID-19 vaccine	Permitted. COVID-19 vaccination should not be given for 72 hours prior to administration of the first dose of AZD8853 or during the DLT period.

Abbreviations: DLT = dose limiting toxicity; G-CSF = granulocyte colony stimulating factor, COVID-19 = coronavirus disease 2019.

6.6 Dose Modification

If, in the opinion of the Investigator, a participant experiences a clinically significant and/or

unacceptable adverse reaction, then the dose may be temporarily or permanently halted.

Supportive therapy will be administered as required. Relevant reporting and discussion with the Study Physician will take place before resumption of dosing.

See the relevant Substudy for details on dose modification.

6.7 Intervention after the End of the Study

No intervention is planned after the end of the study. However, provisions will be in place for participants still enrolled at the end of the study to continue to receive study intervention if, in the opinion of the Investigator, they are continuing to receive benefit from treatment. Such participants will continue to be monitored for all SAEs up to 90 days after the last dose of study intervention, or until commencing new anti-cancer therapy, whichever is sooner.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participants currently receiving treatment with study intervention may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any participant who would be proposed to move to such a study would be asked to sign a new ICF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety to the end of the 90-day follow-up period (Section 8.2.7), or withdrawal of consent or starting another anti-cancer therapy, whichever is earlier. Participants will be evaluated for efficacy until documented disease progression or withdrawal of consent, whichever is earlier. Participants will be followed for subsequent anti-cancer therapy until withdrawal of consent or death, whichever is earlier. See the relevant Substudy SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

The participant should continue attending subsequent study visits and data collection should continue according to the CSP. If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant for the follow-up visit, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Participants may be discontinued from study intervention in the following situations:

- Objective disease progression assessed by Investigator (a confirmatory scan for disease progression is up to the Investigator's discretion).

  Note: If the participant has been discontinued from the AZD8853 intervention before disease progression, it is required for disease assessment to continue (see the relevant Substudy SoA), until documented disease progression.
- Adverse event as defined in Section 8.3.
- Participant or Investigator decision. The participant is free to discontinue treatment at any time, without prejudice to further treatment. When the reason does not impact safety, the Study Physician together with the Investigator will consider the risk/benefit to the participant of stopping treatment.
- Pregnancy (see Section 8.3.10).
- Non-compliance with the CSP (Investigator or participant).

- Participant incorrectly initiated on study treatment.
- Unexpected, significant, or unacceptable risk to the participants enrolled in the study.
- Sponsor termination of study for reasons including but not limited to unfavourable risk/benefit or change in drug development plan.

7.1.1 Temporary Discontinuation

Applicable criteria and procedures for stopping and re-starting study intervention will be defined in individual Substudies.

7.2 Participant Withdrawal from the Study

All participants will be followed until either death, lost to follow-up, or withdrawal of consent, or end of study whichever occurs first.

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team. Please refer to Appendix C for further details.

Participants who are withdrawn from the study but are evaluable per the definition in the Populations for Analyses section of the relevant Substudy will not be replaced.

In addition, participants will be withdrawn from the study in the event that the Sponsor terminates this study.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as described in Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA for the relevant Substudy. Protocol waivers or exemptions are not allowed for any of the Substudies.
- Immediate safety concerns should be discussed with the Study Physician immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

RECIST v1.1 guidelines for measurable, non-measurable, TLs and NTLs, and the objective tumour response criteria are presented in Appendix F of this CSP. Tumour assessments will be based on RECIST v1.1 (Eisenhauer et al, 2009) and will be performed according to the schedule presented in each Substudy.

Standard radiographic imaging using RECIST is used to assess both response (in participants with measurable disease) and progression. An ORR as per RECIST v1.1 criteria requires confirmation of PR and CR and must occur no fewer than 4 weeks after initial documentation of PR or CR. Disease progression will be defined as per RECIST v1.1; however, if the participant is clinically stable, a confirmatory scan for progression is left up to the discretion of the Investigator.

Tumour assessments use images from CT (preferred) or MRI, with i.v. contrast, of the chest, abdomen, and pelvis, and should additionally investigate areas that may be involved based on signs and symptoms of individual participants, collected during screening/baseline and at regular (follow-up) intervals during study intervention. Brain scans (MRI preferred) are mandatory at screening/baseline for all NSCLC participants in this study, participants with known brain metastasis, and as clinically indicated for other participants. Post-baseline MRI of the brain will only have to be performed in participants with brain metastases at baseline, while participants without brain metastases do not need additional brain scans for subsequent tumour assessments unless clinically indicated. The imaging modality used for baseline

tumour assessment should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumour assessment schedule as closely as possible (refer to the SoA in the respective Substudy) relative to dose of study intervention.

Screening/baseline imaging should be performed no more than 28 days before start of study intervention and ideally should be performed as close as possible to and prior to the start of study intervention. Scans obtained as part of standard clinical practice, prior to informed consent, but within the 28-day period are acceptable. Tumour assessments should be performed per the SoA in the respective Substudy until objective disease progression as defined by RECIST v1.1 (refer to Appendix F) and assessed by the Investigator, or withdrawal of consent. Response (CR or PR) should be confirmed by a repeat, consecutive scan at least 4 weeks after the first documentation of response.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment until the Investigator reassesses the participant's status at the next scheduled assessment (confirmation), or sooner if clinically indicated. Scans confirming progression should not be conducted within 1 week after a progression biopsy to allow for reduction in inflammation.

If scans are performed outside of scheduled visit window and the participant has not progressed, every attempt should be made to perform the subsequent scans at their scheduled visits whilst the participant remains on study treatment. If the participant interrupts treatment or incurs a treatment delay, scans should continue to occur at the protocol-defined frequency. It is important to follow the SoA as closely as possible.

Tumour markers will not be used for tumour response assessments as per RECIST v1.1. Tumour markers should be obtained as per standard-of-care.

Storage of Scans

Sites will be required to store electronic copies of all scans (CT, or other scans for efficacy, and PET scans), and the Sponsor will arrange for centralized storage of all imaging data. All imaging assessments, including unscheduled visit scans, will be collected on an ongoing basis, and sent to the Sponsor or designee for storage. The centralized storage of imaging data would allow independent centralized third party blinded review of disease assessments. In this regard, and at the discretion of the Sponsor, an independent central review of all scans used in the assessment of tumours by RECIST v1.1 may be conducted. Guidelines for imaging collection and storage will be provided in a separate document.

Skeletal Muscle Index

To study the effects of AZD8853 on cancer cachexia, SMI will also be collected in this study. To collect this information, participants should have CT or MRI scan with slices at T12 or L3 (Yang et al, 2021,Wang et al, 2020, Rybar et al, 2016). These should be obtained using the same modality and at the same timepoint as the disease assessment scans.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the respective Substudy SoA and are detailed below.

8.2.1 Physical Examinations

Physical examination will be performed at timepoints as specified in the respective Substudy SoA.

- Demographics will be performed at the screening visit.
- A full physical examination should be completed at screening, other SoA specific study visits and EOT and will include, at a minimum: the general appearance of the participant, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Height will be assessed at screening only.
- Investigators should pay special attention to clinical signs related to previous serious illnesses and new or worsening abnormalities that may qualify as AEs. Investigators must ask about participant's appetite (poor, average, or good) at every physical examination and should ask about changes in appetite (worse, about the same, or improved) since the last assessment for all physical examinations after screening.
- A standard medical, medication, and surgical history including smoking history (smoking pack-years) will be obtained with review of the selection criteria with the participant.

8.2.2 ECOG Performance Status

Performance status will be assessed at timepoints as specified in the respective Substudy SoA according to ECOG criteria as follows:

- 0 = Fully active, able to carry out all pre-disease activities without restrictions.
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature eg, light housework, office work.
- 2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.

- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.
- 5 = Dead

8.2.3 Vital Signs

Vital signs measurements (body temperature, BP, heart [pulse] rate, respiration rate, and body weight) will be performed at timelines specified in the respective Substudy SoA.

- Blood pressure and pulse/heart rate measurements will be assessed in supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure, respiratory rate, and pulse measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting.
- Vital signs are to be taken before any blood collection.
- Body temperature will be taken prior to all infusions (within 2 hours before start of the infusion).
- Body weight is only required pre-dose.

8.2.4 Electrocardiograms

Electrocardiograms will be performed at timepoints specified in the respective Substudy SoA.

Local 12-lead digital ECGs will be obtained after the participant has been resting semi-supine for at least 10 minutes. Triplicate ECGs will be collected within a 5-minute period. All ECGs should be recorded with the participant in supine position.

If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. If a clinically significant abnormal ECG finding occurs on study, the Investigator should contact the Study Physician.

The ECG parameters to be determined will include (but will not be limited to) the following:

- Heart rate
- RR interval: duration in msec between 2 R peaks of 2 consecutive QRS complexes
- PR interval: duration in msec from the beginning of wave P to onset of ventricular depolarisation (Q and R)
- QRS interval: duration in msec of the QRS complex
- QT interval: duration in msec from the beginning of Q wave to the end of the T-wave

- QTcF: QT[msec]/RR[sec]1/3

Any abnormal finding in the ECG tracing will be evaluated by the Investigator and will be specifically documented and registered in the eCRF. Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded in the AE eCRF.

8.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, virology, and urinalysis will be taken at the timepoints indicated in the respective Substudy SoA.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date of collection and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The analysis of safety samples will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

For all participants, results of safety laboratory testing (haematology, coagulation and clinical chemistry at a minimum) must be available within 24 hours prior to dosing and must be reviewed by the Investigator prior to administration of AZD8853. Samples can be collected the day before AZD8853 administration. If clinically indicated, additional clinical laboratory tests and evaluations may be performed by the Investigator and these need to be entered into the eCRF.

The laboratory variables to be measured for haematology, clinical chemistry, urinalysis, coagulation, virology, and pregnancy testing are listed in Table 10.

Table 10 Laboratory Safety Variables

Haematology (whole blood)		**Clinical Chemistry (serum or plasma)**		
B-Hb		S/P-Creatinine	S/P-Chloride	
B-WBC count with differential		S/P-Bilirubin total	S/P-Magnesium	
B-Platelet count		S/P-Direct and indirect bilirubin	S/P-Phosphorus	
B-Haematocrit		S/P-Alkaline phosphatase	S/P-Cholesterol	
B-Absolute neutrophil count		S/P-Aspartate transaminase	S/P-Amylase	
B-Absolute lymphocyte count		S/P-Alanine transaminase	S/P-Lipase	
		S/P-Albumin	S/P-TSH	
Urinalysis (dipstick)		S/P-Free T3	S/P-Free T4	
Colour and appearance		S/P-Potassium	S/P-Bicarbonate	
U-Hb/Erythrocytes/Blood	U-Protein/Albumin	S/P-Calcium, total	S/P-Total protein	
U-Glucose	U-pH	S/P-Sodium	S/P-Blood urea nitrogen	
U-Specific gravity	U-Ketones	S/P-Creatine phosphokinase	S/P-Glucose (fasting preferred)	
U-Microscopy including WBC/high-power field, RBC/high-power field [a]		S/P-HbA1c	S/P-Triglycerides	
		S/P-lactate dehydrogenase		
Coagulation				
INR	PT	aPTT, absolute or relative	D-Dimer	Fibrinogen
Virology				
Hepatitis B virus core antibodies		Hepatitis A serology		
Hepatitis C serology		HIV-1 and 2 antibodies		
Hepatitis B virus surface antigen				
Pregnancy Test (women of childbearing potential only)				
β-hCG				

[a] Microscopy should be performed at Investigator's discretion for abnormal dipstick.
Abbreviations: aPTT = activated partial thromboplastin time; B = blood; Hb = haemoglobin; HbA1c = haemoglobin A1c; hCG = human chorionic gonadotropin; HIV = human immunodeficiency viruses; INR = international normalised ratio; P = plasma; PT = prothrombin time; RBC = red blood cells; S = serum; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; U = urinalysis; WBC = white blood cells.

8.2.6 30-Day Follow-up Visit

A follow-up visit will be performed 30 (± 7) days from the EOT visit (see the SoA for the relevant Substudy).

8.2.7 90-Day Follow-up Visit

A follow-up visit will be performed 90 (± 7) days from the time that all study intervention is permanently discontinued (see the SoA for the relevant Substudy). Assessment of disease progression (CT or MRI) will not be performed at this visit if previously confirmed disease progression has been documented.

8.2.8 Survival Follow-up

All participants will be followed for survival until death, lost to follow-up, withdrawal of consent, or end of study whichever occurs first. Participants will be followed for survival by telephone calls, email, or clinic visits approximately every 12 weeks. During this period, information will be collected in the eCRF on survival status and any new anti-cancer therapies, and on any SAEs considered related to study intervention or study procedures.

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs/SAEs will be collected from the time of signature of the screening ICF throughout the treatment period and including the follow-up period of 90 days (± 7 days) after last dose of study intervention.

If the Investigator becomes aware of any SAE, including death, at any time during survival follow-up, with a suspected causal relationship to the study intervention, the Investigator shall report the SAE in the eCRF.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant’s last assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the

eCRF. These AEs must still be reported to the Sponsor and records must be kept with the participant's record. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- CTCAE grade/changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome, including administration of any treatment

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The Investigator should assess causal relationship between study intervention and each AE, 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 IMP?'

For SAEs, causal relationship should also be assessed for all other study 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 B to the CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant 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.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated physical examinations, laboratory values, vital signs, ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

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 unless unequivocally related to disease progression.

8.3.6 Adverse Events of Special Interest

An AESI is an AE of scientific and medical interest specific to understanding of a study intervention and may require close monitoring and rapid communication to AstraZeneca by the Investigator. An AESI may be serious or non-serious. The reporting of AESIs allows ongoing surveillance of these events to characterise and understand them in association with

the use of a study intervention.

Adverse events of special interest will be recorded in the eCRF using a recognised medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the Investigator for severity, relationship to the study intervention, possible aetiologies, and whether the event meets criteria for an SAE and therefore requires immediate notification to AstraZeneca. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported as described in Section 8.3.9.

Based on the available preclinical data, review of the cumulative literature, and biological plausibility, the following events are considered to be AESIs:

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

Other AEs which are considered to be AESIs with AZD8853 include, but are not limited to:

- CCI
- CCI
- CCI
- CCI

The immune system can respond to foreign protein, even to humanised mAb by producing human-anti-human antibodies, which may result in formation of immune complexes and their deposition in blood vessels, joints, and glomeruli causing symptomatic disease (eg, CCI). Participants will be monitored clinically and for the presence of ADAs. Participants who experience an AE suspected to be immune complex related will discontinue study intervention. Immune complex disease will be managed in accordance with standard-of-care.

- CCI

CCI . CCI have some common manifestations and may be difficult to distinguish from each other.

[redacted] are commonly observed during or shortly after the first time of exposure to therapeutic mAbs delivered through i.v. infusion. These reactions are less common following subsequent exposures. Unlike [redacted], [redacted] is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by [redacted]. The Investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to AZD8853 and consider the above-mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of study intervention are to be judged by the Investigator at his/her own discretion. For the Investigator's convenience and to facilitate consistency in judgements, a copy of the [redacted] is provided in Appendix H. Refer to TMGs for management of participants with [redacted] (including [redacted]) and [redacted]. In the event of an [redacted], the site should document which medications have been infused at the time of onset of the [redacted] in addition to signs and symptoms.

8.3.7 Hy's Law

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

8.3.8 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the study intervention is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. 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 AEs during the study.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, 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 one 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 AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 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 EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

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

For further guidance on the definition of a SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for AZD8853.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the participant has received any study intervention.

If a pregnancy is reported, the Investigator should inform AstraZeneca within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. 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 anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy 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 provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and 3 months following the last dose (see inclusion criteria, Section 5.1).

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 3 months after the last dose should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

If a pregnancy occurs in a participant's partner within the timeframe specified above, then Investigators or other site personnel will inform the appropriate Sponsor representative immediately, or no later than 24 hours of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

8.3.11 New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study intervention and have been identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.3.12 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of the last dose of study intervention, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the eCRF. The report should contain a comment regarding the

co-involvement of progressive disease, if appropriate, and should assign main and contributory causes of death.

- Death with an unknown cause should always be reported as an SAE. It should also be documented in the eCRF. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.
- Deaths occurring after the protocol-defined safety follow-up period (90 days) after the administration of the last dose of study intervention should be documented in the eCRF. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.3.13 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 will work with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of study intervention greater than the dose that was intended to be given will be considered an overdose. All overdoses should be recorded as follows:

- 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 drug occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all

relevant information is provided to the AstraZeneca Patient Safety data entry site **within 24 hours** for overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised. Additional analyses may be conducted on the anonymised, PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of AZD8853 as specified in the SoA of relevant Substudies.
- Samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Serum samples will be used to analyse the PK of AZD8853. Samples collected for analyses of AZD8853 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Refer to relevant Substudy for the sampling schedule for PK samples.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Tiered analyses will be performed to include screening, confirmatory, and titre assay components. Full details of the methods used will be described in a separate report. ADA samples may also be further tested for characterization of the ADA response, including possible assessment of neutralising antibody. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Refer to relevant Substudy for the sampling schedule for ADA samples.

8.5.3 Pharmacodynamics

Refer to relevant Substudy for information on pharmacodynamics.

8.6 CCI [redacted]

Refer to relevant Substudy for information on CCI [redacted].

8.7 CCI [redacted] Initiative Sample

Collection of CCI [redacted] is also part of this study as specified in the SoA and is subject to agreement in the ICF addendum.

Blood sample for CCI [redacted] will be collected from participants who have consented to participate in the CCI [redacted] of the study. Participation is optional. Participants who do not wish to participate in the CCI [redacted] may still participate in the study.

See Appendix D for information regarding the CCI [redacted]. Details on processes for collection and shipment and destruction of these samples can be found either in

the appendices or in the Laboratory Manual.

For storage and destruction of CCI see Appendix D.

8.8 CCI

Participants will be given the option to complete a CCI after consenting to the main study to collect CCI The goals of this CCI research are to CCI . Certain main study data not related to disease or treatment, such as demographics, informed consent review metrics, etc., may be re-used from the EDC and/or eConsent platform. This CCI does not collect clinical data about the participant's disease, symptoms, treatment effect or adverse events. Therefore, data from this CCI will not be reported in the CSR. The data will be anonymized and aggregated and may be published in an academic journal or presented at scientific meetings. No individual, identifying, protected health information will be included in any publications or presentations.

9 STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by AstraZeneca or a CRO under the direction of the Early Biometrics Oncology, AstraZeneca. A comprehensive SAP will be prepared.

9.1 Statistical Hypotheses

Refer to the relevant Substudy for information.

9.2 Sample Size Determination

Refer to the relevant Substudy for information.

9.3 Populations for Analyses

For purposes of analysis, the study populations are defined as provided in Table 11. For all efficacy analyses, and for baseline and demography, participants will be classified according to the dose they were assigned to (ie, the planned treatment).

Table 11 Populations for Analyses

Population/Analysis Set	Description	Endpoint/Output
Enrolled	All participants who sign the ICF.	Disposition
Safety	All participants who receive at least one dose of study intervention.	Exposure Safety endpoints PFS OS ctDNA
DLT Evaluable	Enrolled participants who complete the DLT evaluation period (defined as 21 days after receiving the first infusion of study intervention and has completed safety evaluation requirements) with at least 75% dosing or who experience any DLT.	DLT
Response Evaluable	All dosed participants who have measurable disease at baseline.	ORR DoR DCR Tumour size
Pharmacokinetics	All participants who receive at least one dose of study intervention with at least one reportable concentration.	PK concentrations PK parameters
Immunogenicity	All participants who receive at least one dose of study intervention with at least one reportable immunogenicity measurement.	Immunogenicity endpoints

Abbreviations: ctDNA = circulating tumour deoxyribonucleic acid; DCR = disease control rate; DLT = dose limiting toxicity; DoR = duration of response; ICF = informed consent form; PFS = Progression Free Survival; PK = pharmacokinetics; OS = overall survival; ORR = objective response rate.

9.4 Statistical Analyses

The SAP will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section only includes the planned statistical analyses for the master objectives.

Refer to the relevant Substudy for more information on the statistical analyses for Substudy-specific objectives.

9.4.1 General Considerations

Descriptive statistics will be used for all variables. 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 based on the population total.

Time to event variables will be presented using the Kaplan-Meier methodology, including median time calculated from the Kaplan-Meier curves.

In general, the last observed measurement prior to first dose of study intervention will be considered the baseline measurement.

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, any impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatment, and other protocol deviations) may be generated. More details will be provided in the SAP.

9.4.2 Safety Analyses

Safety and tolerability will be assessed in terms of DLTs, AEs/SAEs, ECOG status, vital signs, clinical chemistry/haematology parameters, dose interruptions/discontinuations and ECG data. These variables will be collected for all participants. All safety analyses will be performed on the Safety Population, except for the evaluation of DLTs that will be performed on the DLT Evaluable Population. Additional subgroup analysis of safety may be performed, as specified in the SAP.

Medical Dictionary for Regulatory Activities will be used to code AEs. Adverse events will be graded according to the NCI CTCAE v5.0. The number of participants in each dose cohort (Part A) and each expansion (Parts B and C) experiencing each AE will be summarised by MedDRA SOC and preferred term. The number and percentage of participants with AEs in

different categories (eg, causally related, CTCAE Grade ≥ 3, etc) will be summarised by dose regimen; events in each category will be further summarised by MedDRA SOC and preferred term. Serious adverse events will be summarised separately, if a sufficient number occurs.

Adverse event summary tables will include only treatment-emergent AEs. Adverse events will be defined as treatment-emergent if they have an onset or worsen (by Investigator report of a change in intensity) during the study treatment or the safety follow-up period (defined as 90 days after last dose of study treatment) but prior to subsequent anti-cancer therapy. Adverse events occurring outside this period will only be listed.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and BP)/ECG data will be performed for identification of OAEs. Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

Duration of exposure will be summarised.

All safety data including clinical chemistry, haematology, coagulation, urinalysis, vital signs, and ECG data will be listed individually by participant and appropriately summarised. For all laboratory variables that are included in the current version of CTCAE, the CTCAE grade will be calculated. Details of any deaths will be listed for all participants. Graphical presentations of safety data will be presented as appropriate. Dose-limiting toxicities will be displayed in a listing.

9.4.3 Efficacy Analyses

The efficacy endpoints for tumour response (ORR, DCR at 15 weeks, DoR, and percentage change in tumour size) will be summarised for the Response Evaluable Population using RECIST v1.1 by Investigator assessment. The efficacy endpoints of PFS and OS will be summarised on the Safety Population.

Additional subgroup analysis of efficacy may be performed as specified in the SAP.

The RECIST tumour response data will be used to programmatically determine each participant's visit response and derive the endpoints ORR, DoR, DCR at 15 weeks, percentage change in tumour size, and PFS.

Best Overall Response

The BoR is calculated based on the overall visit responses from each RECIST assessment. It is the best response a participant has following start of treatment but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST using the following response categories: CR, PR, SD, progressive disease, and NE.

Objective Response Rate

The ORR is defined as the percentage of participants with a confirmed CR or PR, with the denominator defined as the number of participants in the Response Evaluable Population. Objective response rate and its 90% CIs (Clopper Pearson method; Clopper et al, 1934) will be summarised.

Duration of Response

The DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression or death in the absence of disease progression. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR that was subsequently confirmed. Participants 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.

It will be summarised using descriptive statistics and Kaplan-Meier plots, where there are sufficient numbers of responders.

Disease Control Rate at 15 Weeks

The DCR at 15 weeks is defined as the percentage of participants who have a BoR of CR or PR in the first 16 weeks (to allow for late assessment within the assessment window) or who have SD for at least 14 weeks after the start of treatment (to allow for early assessment within the assessment window). The DCR and its 90% CIs (Clopper Pearson method; Clopper et al, 1934) will be summarised.

Percentage Change in Tumour Size

The percentage change in TL tumour size from baseline will be summarised using descriptive statistics by timepoint. Best percentage change will also be summarised.

Waterfall plots showing the percentage change at 15 weeks and the best percentage change from baseline in sum of the diameters of TLs will be produced. Spider plots showing the percentage change from baseline in tumour size for each participant over time will be produced.

Progression-free Survival

The PFS is defined as the time from the start of study intervention until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the participant withdraws from study intervention or receives another anti-cancer therapy prior to progression. Participants 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.

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

The 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 participants for PFS, the participant will be censored at the latest of the dates contributing to a particular overall visit assessment.

Progression-free survival will be summarised descriptively, and Kaplan-Meier plots will be provided.

Overall Survival

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

Overall survival will be summarised descriptively, and Kaplan-Meier plots will be provided.

Change in ctDNA

Percentage change in ctDNA from baseline to each post baseline timepoint as well as the maximum change will be analysed descriptively on the Safety Population.

9.4.4 Other Analyses

9.4.4.1 Immunogenicity, Pharmacokinetics and Pharmacodynamics

The PK analysis of the serum data for AZD8853 will be performed on the PK Population. The actual sampling times will be used in the parameter calculations and the PK parameters will be derived using standard non-compartmental methods, if the data permits. It is anticipated that Cmax, AUC, and other PK parameters will be calculated if the data allows.

Relevant descriptive statistics will be used to summarise PK parameters and concentrations. In addition, population PK modelling may be conducted and reported separately.

Immunogenicity results will be analysed descriptively on the Immunogenicity Population by summarising the number and percentage of participants who develop detectable ADAs against AZD8853 at protocol-specified timepoints. The immunogenicity titre may be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, efficacy, and safety may be evaluated, if the data allow.

Refer to the relevant Substudy for information on PD analyses. Further details on the analysis of immunogenicity, PK and PD will be provided in the SAP.

9.5 Interim Analyses

Interim analyses will be conducted separately for each Substudy and are described in the relevant Substudy.

9.6 Safety Review Committee

A study-specific SRC will be responsible for making dose-escalation or dose de-escalation decisions and recommendations regarding further conduct of the study, during all parts of the study. The SRC will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data to monitor the ongoing safety profile of the study intervention.

The SRC may also meet to review data at other timepoints (eg, in response to AEs assessed as medically relevant by the Study Physician). The SRC will review the totality of the AE, SAE, and laboratory safety data from a minimum of 3 participants who have completed the 21-day DLT period, and all relevant available data, including PK, prior to adjudicating on dose-escalation/de-escalation decisions based on the dose-escalation rules. For each dose cohort, every effort will be made to have all available PK data to the SRC at the time of the dose escalation decision. All decisions by the SRC will be documented and shared with all participating sites in writing. The SRC will be composed of Sponsor representatives and Investigators. The composition and procedures of the SRC will be fully described in the SRC charter.

10 SUBSTUDY 1

10.1 Substudy 1 Summary

10.1.1 Schema

CCI

[redacted]

CCI

[redacted]

10.1.2 Schedule of Activities

Table 12 Schedule of Activities - Screening

Study Period	Screening	Details in Section
Visit Number	**V1**	
Procedure/Study Day	**Days -28 to -1** [a]	
Screening informed consent (Main Study)	X	10.5, Appendix A 3
Assignment of participant identification number (PID / E-Code) in IRT	X	6.3
Metformin Use History, including date of last dose	X	5.2, Table 8
CCI [redacted]	X	8.8
Confirm eligibility for enrolment in Main Study	X	10.5.1; 10.5.2
Medical and Disease History		
Demographics	X	8.2.1
Medical/surgical history, including smoking history	X	8.2.1
Disease history and characteristics, including biomarkers and CCI [redacted]	X	8.2.1
Prior cancer treatment, including surgeries, radiotherapy, and systemic therapy	X	8.2.1
Disease Assessments		
Disease assessment by RECIST v1.1 and SMI assessment [b]	X [c]	10.8.1
CT or MRI, Brain (Required for NSCLC participants, participants with known brain metastasis, and as clinically indicated for other participants)	X [c]	10.8.1
Study Procedures and Examinations		
Physical examination, including assessment of appetite	X	8.2.1
ECOG performance status	X	8.2.2
Vital signs, including weight	X	8.2.3
Height	X	8.2.1
Local 12-lead ECG (triplicate)	X	8.2.4
Assessment of AEs/SAEs	X	8.3

Study Period	Screening	Details in Section
Visit Number	**V1**	
Procedure/Study Day	**Days -28 to -1** [a]	
Concomitant medications	X	6.5
Safety Laboratories		
Clinical chemistry	X	8.2.5
HbA1c	X	8.2.5
Thyroid function tests (TSH, free T4, free T3)	X	8.2.5
Haematology	X	8.2.5
Urinalysis	X	8.2.5
Serum pregnancy test (WOCBP)	X	8.2.5
Coagulation parameters (PT/aPTT/INR/d-dimer/fibrinogen)	X	8.2.5
Virology (Hepatitis A, B, and C, HIV-1 and HIV-2) [d]	X	8.2.5
Biomarker Evaluations		
CCI	X	10.8.6.2
Part A/C: CCI [e]	X	10.8.6.1.2
Part B: Mandatory paired biopsy [e]	X	10.8.6.1.1
Serum for GDF15 target engagement	X	10.8.5.3.1
Whole blood for CCI (refrigerated)	X	10.8.6.4
Whole blood for flow cytometry	X	10.8.6.5
Whole blood for CCI	X	10.8.6.3
CCI	X	10.8.6.7
CCI	X	10.8.6.7
Plasma for circulating tumour DNA	X	10.8.6.6
Part B only: CD8+ PET (select and validated sites only)		
CD8+ PET tracer administration	X [f]	Appendix I
Whole body PET scan	X [f]	Appendix I

[a] The screening period may last no longer than 28 days from Cycle 1 Day 1.

[b] To include CT or MRI slices through T12 and L3.

[c] Previous scans for baseline disease and brain imaging that were performed within 4 weeks of dosing and meet the protocol requirements do not need to be repeated.

[d] Participants with active hepatitis A, active hepatitis B, or active hepatitis C are excluded; however, participants who have chronic hepatitis B or hepatitis C receiving suppressive antiviral therapy are allowed to be enrolled if ALT is normal and viral load is controlled. Controlled hepatitis B viral load is defined as serum hepatitis B virus DNA < 2000 IU/mL by PCR. Controlled hepatitis C viral load is defined as undetectable hepatitis C RNA by PCR either spontaneously or in response to a successful prior course of anti-hepatitis C therapy. *NOTE*: Participants with controlled hepatitis B viral load must remain on antiviral therapy, per institutional practice, to ensure adequate viral suppression during the study treatment and follow-up period.

[e] Fresh paired biopsy samples will be taken as specified in all mandatory paired biopsy cohorts in Parts B but are optional for all other participants. CCI [redacted]. If they are taken during screening they will not need to be taken for Cycle 1 Day 1 pre-dose.

[f] Whole body PET imaging to occur before the initial dosing of study intervention (≤ 14 day) on Cycle 1 Day 1. Imaging to be done only after the participant's eligibility for the study has been confirmed. PET imaging must be before pre-treatment biopsy. CD8+ PET Tracer [^{89}Zirconium (Zr)-deferoxamine (Df)-crefmirlimab] to be ordered at least 72 hours before administration and PET imaging appointments should be booked accordingly. Tracer to be administered preferably 24 (±3) hours but not more than 72 hours prior to whole body PET imaging. The duration between administration of the tracer and the PET scan should be the same at screening and at Day 29. If a participant holds or discontinues study treatment prior to Day 29, if able, the participant should still perform the PET scan as scheduled.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; CD8 = cluster of differentiation 8; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GDF15 = growth differentiation factor 15; HbA1c = haemoglobin A1c; HIV = human immunodeficiency virus; IRT = interactive response technology system; INR = international normalised ratio; MRI = magnetic resonance imaging; NSCLC = non-small-cell lung carcinoma; CCI [redacted] cell; PET = positron emission tomography; PT = prothrombin time; PID = participant identification number; RECIST = response evaluation criteria in solid tumours; RNA = ribonucleic acid; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; V = visit; WOCBP = woman of childbearing potential.

Table 13 Schedule of Activities – Study Visits

Visit Number	V2		V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13-Vn	Details in Section
Procedure/Study Day	**D1 Pre-Dose**	**D1 Post-Dose**	**D2**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D64**	**D85**	**D106**	**D127+ Q3W**	
Week	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19+**	
Cycle Number and Cycle Day [a]	**C1D1** [b]	**C1D1**	**C1D2**	**C1D8 (±1D)**	**C1D15 (±1D)**	**C2D1 (±1D)**	**C2D8 (±1D)**	**C2 D15 (±1D)**	**C3D1 (±3D)**	**C4D1 (±3D)**	**C5D1 (±3D)**	**C6D1 (±3D)**	**C7D1-CnD1 (±3D)**	
Eligibility														
Confirm eligibility for enrolment in Main Study	X													10.5.1; 10.5.2
Study Procedures and Examinations														
Physical examination, including appetite assessment	X			X	X	X	X [c]	X [c]	X	X	X	X	X	8.2.1
Local 12-lead ECG	X	X				X			X				X Q12W	10.8.2.1 Table 17
Vital signs, including body weight	X	X [d]		X	X	X	X [c]	X [c]	X	X	X	X	X	8.2.3
ECOG Performance Status	X			X	X	X	X [c]	X [c]	X	X	X	X	X	8.2.2
Assessment of AEs/SAEs	X	X	X	X	X	X	X [c]	X [c]	X	X	X	X	X	8.3

Visit Number	**V2**		**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13-Vn**	**Details in Section**
Procedure/Study Day	**D1 Pre-Dose**	**D1 Post-Dose**	**D2**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D64**	**D85**	**D106**	**D127+ Q3W**	
Week	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19+**	
Cycle Number and Cycle Day [a]	**C1D1** [b]	**C1D1**	**C1D2**	**C1D8 (±1D)**	**C1D15 (±1D)**	**C2D1 (±1D)**	**C2D8 (±1D)**	**C2 D15 (±1D)**	**C3D1 (±3D)**	**C4D1 (±3D)**	**C5D1 (±3D)**	**C6D1 (±3D)**	**C7D1-CnD1 (±3D)**	
Concomitant medications	X		X	X	X	X	X [c]	X [c]	X	X	X	X	X	6.5
Disease Assessments														
Disease assessment by RECIST v1.1 and SMI assessment [e]								X W6 D1-D7				X [f] W15 D1-D7	W24±6D then Q9W±6D until W52, then Q12W±6D	10.8.1
CT or MRI, Brain (required for participants with known brain metastasis and as clinically indicated for other participants)								X W6 D1-D7				X [f] W15 D1-D7	W24±6D then Q9W±6D until W52, then Q12W±6D	10.8.1
Safety Laboratories														
Clinical chemistry [b]	X			X	X	X			X	X	X	X	X	8.2.5
HbA1c										X			X Q12W	8.2.5
Thyroid function (TSH, free T4, free T3) [b, i]	X					X			X	X	X	X	X	8.2.5

Visit Number	**V2**		**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13-Vn**	**Details in Section**
Procedure/Study Day	**D1 Pre-Dose**	**D1 Post-Dose**	**D2**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D64**	**D85**	**D106**	**D127+ Q3W**	
Week	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19+**	
Cycle Number and Cycle Day [a]	**C1D1** [b]	**C1D1**	**C1D2**	**C1D8 (±1D)**	**C1D15 (±1D)**	**C2D1 (±1D)**	**C2D8 (±1D)**	**C2 D15 (±1D)**	**C3D1 (±3D)**	**C4D1 (±3D)**	**C5D1 (±3D)**	**C6D1 (±3D)**	**C7D1-CnD1 (±3D)**	
Haematology [b]	X			X	X	X			X	X	X	X	X	8.2.5
Urinalysis [b]	X					X			X	X	X	X	X	8.2.5
Pregnancy test (WOCBP Only) [j]	X					X			X	X	X	X	X	8.2.5
Coagulation parameters (PT/aPTT/INR/d-Dimer/fibrinogen) [b]	X			X	X	X			X	X	X	X	X	8.2.5
Virology (Hepatitis B and C) [k]											X Q12W			8.2.5
Biomarker Evaluations [g]														
Part A/C: CCI	X [l]					X [m]	X [m]							10.8.6.1.2
Part B: Mandatory paired biopsy	X [l]					X [m]	X [m]							10.8.6.1.1
Serum for GDF15 target engagement	X	X	X	X	X	X	X [n]		X	X	X	X		10.8.5.3.1, Table 20
Whole blood for CCI (refrigerated)	X						X [n]						On progression	10.8.6.4

Visit Number	V2		V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13-Vn	Details in Section
Procedure/Study Day	**D1 Pre-Dose**	**D1 Post-Dose**	**D2**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D64**	**D85**	**D106**	**D127+ Q3W**	
Week	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19+**	
Cycle Number and Cycle Day [a]	**C1D1** [b]	**C1D1**	**C1D2**	**C1D8 (±1D)**	**C1D15 (±1D)**	**C2D1 (±1D)**	**C2D8 (±1D)**	**C2 D15 (±1D)**	**C3D1 (±3D)**	**C4D1 (±3D)**	**C5D1 (±3D)**	**C6D1 (±3D)**	**C7D1-CnD1 (±3D)**	
Whole blood for flow cytometry	X			X		X	X [n]		X	X	X		On progression	10.8.6.5
CCI [redacted]	X			X		X	X [n]		X				On progression	10.8.6.3
CCI [redacted]	X			X		X	X [n]		X	X	X		On progression	10.8.6.7
CCI [redacted]	X			X		X	X [n]		X	X	X		On progression	10.8.6.7
Plasma for circulating tumour DNA	X			X		X	X [n]		X	X	X		On progression	10.8.6.6
CCI [redacted] [h]	X													8.7
PK and Immunogenicity														
Part A: AZD8853 PK	X	X	X	X	X	X	X [n]		X	X	X	X		10.8.5.1; Table 18
All Parts: AZD8853 ADA	X [g]					X [g]			X [g]		X [g]		X [g] Q12W	10.8.5.2; Table 19
Part B: AZD8853 PK	X	X	X	X	X	X			X	X	X	X		10.8.5.1; Table 18

Visit Number	V2		V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13-Vn	Details in Section
Procedure/Study Day	**D1 Pre-Dose**	**D1 Post-Dose**	**D2**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D64**	**D85**	**D106**	**D127+ Q3W**	
Week	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19+**	
Cycle Number and Cycle Day [a]	**C1D1** [b]	**C1D1**	**C1D2**	**C1D8 (±1D)**	**C1D15 (±1D)**	**C2D1 (±1D)**	**C2D8 (±1D)**	**C2 D15 (±1D)**	**C3D1 (±3D)**	**C4D1 (±3D)**	**C5D1 (±3D)**	**C6D1 (±3D)**	**C7D1-CnD1 (±3D)**	
Part C: AZD8853 PK	X	X				X			X	X	X	X		10.8.5.1; Table 18
Study Treatment Administration														
AZD8853 administration (Q3W)	X					X			X	X	X	X	Q3W	6.1
Part B only: CD8+ PET (select and validated sites only)														
CD8+ PET Tracer Administration							X [o]							Appendix I
Whole body PET scan							X [o]							Appendix I

[a] Any timing of safety assessment visit is relative to the day of most recent dosing (Day 1 of the latest cycle).
[b] If screening assessments have been performed within the 72 hours prior to Day 1, then the assessment does not need to be performed pre-dose on Day 1. All safety laboratory results must be reviewed by the Investigator or physician designee prior to administration of the scheduled dose of study intervention. Pregnancy testing for WOCBP is required on all days of dosing.
[c] For Part A only.
[d] Weight on Day 1 post-dose is not needed.
[e] To include CT or MRI slices through T12 and L3. Any timing of tumour assessment visit is relative to Cycle 1 Day 1.
[f] Disease assessment should be performed on the week prior to next assessment cycle, always prior to dosing.
[g] All collections must be pre-dose unless specified otherwise.
[h] Sample can be taken at any point during study.
[i] Free T4 and T3 measured if TSH is abnormal or if clinical suspicion of an AE related to the endocrine system.
[j] A urine or serum pregnancy test is acceptable; if urine test is equivocal or positive then serum β-hCG testing should be performed for confirmation.
[k] Required for participants with a history of hepatitis B or hepatitis C.

[l] Fresh paired biopsy samples will be taken as specified in all mandatory paired biopsy cohorts in Parts B but are optional for all other participants. [redacted]. If they are taken during screening they will not need to be taken for Cycle 1 Day 1 pre-dose.

[m] The second paired biopsy sample should be collected on Cycle 2 Day 8 (±[redacted] days relative to Cycle 2 Day 8). For participants who are in the CD8+ PET cohort, the first and second biopsy should be taken within [redacted] hours after the first and second CD8+ PET scan, respectively. This second biopsy must still be collected if not done within the time windows described.

[n] To be taken at time of second paired biopsy.

[o] Whole body PET imaging to occur before the initial dosing of study intervention (≤ 14 day) on Cycle 1 Day 1. Imaging to be done only after the participant's eligibility for the study has been confirmed. PET imaging must be before pre-treatment biopsy. CD8+ PET Tracer [^{89}Zirconium (Zr)-deferoxamine (Df)-crefmirlimab] to be ordered at least 72 hours before administration and PET imaging appointments should be booked accordingly. Tracer to be administered preferably 24 (±3) hours but not more than 72 hours prior to whole body PET imaging. The duration between administration of the tracer and the PET scan should be the same at screening and at Day 29. If a participant holds or discontinues treatment prior to Day 29, if able, the participant should still have the PET scan as scheduled.

Abbreviations: ADA = antidrug antibody; AE = adverse event; CR = complete response; CT= computed tomography; D = Day; DNA= deoxyribonucleic acid; ECG = electrocardiogram; ECOG = eastern cooperative oncology group; EOT = end of treatment; GDF15 = growth differentiation factor 15; HbA1c = haemoglobin A1c; MRI = magnetic resonance imaging; n = visit number; NSCLC = non-small-cell lung cancer; [redacted]; PK = pharmacokinetic; PR = partial response; Q3W = every 3 weeks; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q26W = every 26 weeks; RNA = ribonucleic acid; RECIST = response evaluation criteria in solid tumours; SAE = serious adverse event; SD = stable disease; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; V = visit; WOCBP = woman of childbearing potential.

Table 14 Schedule of Activities – End of Treatment

Study Period	EOT	Follow-up Post EOT		LTFU	Details in Section
Procedure/Study Day		Day 30 (± 7 days)	Day 90 (± 7 days)	Q12W Post Day 90 Visit	
		Post EOT	Post Last Dose		
Study Procedures and Examinations					
Physical examination, including appetite assessment	X	X	X		8.2.1
ECOG performance status	X	X	X		8.2.2
Local 12-lead ECG (triplicate)	X				8.2.4
Vital signs, including body weight	X	X	X		8.2.3
Assessment of AEs/SAEs	X	X	X		8.3
Concomitant medications	X	X	X		6.5
Disease Assessments					
Disease assessment by RECIST v1.1 and SMI assessment [a]	X [b]		X [c]	X [c]	10.8.1
CT or MRI, brain (Required for participants with known brain metastasis and as clinically indicated for other participants)	X [b]		X [c]	X [c]	10.8.1
Safety Laboratories					
Clinical chemistry	X	X			8.2.5
Haematology	X	X			8.2.5
HbA1c	X	X			8.2.5
Thyroid function tests (TSH, free T4, free T3) [d]	X	X			8.2.5
Urinalysis	X	X			8.2.5
Coagulation parameters (PT/aPTT/INR/d-Dimer/Fibrinogen)	X	X			8.2.5
Pregnancy test (WOCBP) [e]	X	X	X		8.2.5
Virology (Hepatitis B and C) [f]		X			8.2.5
Biomarker Evaluations					
CCI [redacted]	Collect on progression				10.8.6.1.3

Study Period	EOT	Follow-up Post EOT		LTFU	Details in Section
Procedure/Study Day		Day 30 (± 7 days)	Day 90 (± 7 days)	Q12W Post Day 90 Visit	
		Post EOT	Post Last Dose		
Serum for GDF15 target engagement	X	X	X		10.8.5.3.1
Whole blood for CCI (refrigerated)	X	X	X		10.8.6.4
Whole blood for flow cytometry	X	X	X		10.8.6.5
CCI	X	X	X		10.8.6.3
CCI	X	X	X		10.8.6.7
CCI	X	X	X		10.8.6.7
Plasma for circulating tumour DNA	X	X	X		10.8.6.6
PK and Immunogenicity					
Parts A, B and C: AZD8853 PK			X		10.8.5.1 Table 18
AZD8853 ADA	X	X	X		10.8.5.2 Table 19
EOT and Follow-up Assessment					
Subsequent anti-cancer therapy	X	X	X	X	8.2.8
Survival status (by telephone, email, or clinic visit)	X	X	X	X	8.2.8

[a] To include CT or MRI slices through T12 and L3.
[b] If CT or MRI scan for disease assessment is performed ≤ 14 days prior to the EOT visit, it will not be required at EOT visit.
[c] Will not be performed if previously confirmed disease progression has been documented.
[d] Free T4 and T3 measured if TSH is abnormal or if clinical suspicion of an AE related to the endocrine system.
[e] A urine or serum pregnancy test is acceptable; if urine test is equivocal or positive then serum β-hCG testing should be performed for confirmation.
[f] Required for participants with a history of hepatitis B or hepatitis C.

Abbreviations: ADA = antidrug antibody; AE = adverse event; aPTT = activated partial thromboplastin time; CT = computerized tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; GDF15 = growth differentiation factor 15; INR = international normalised ratio; LTFU = long Term Follow-up; MRI = magnetic resonance imaging; NSCLC = non-small-cell lung cancer; CCI ; PK = pharmacokinetics; PT = prothrombin time; Q12W = every 12 weeks; RNA = ribonucleic acid; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = woman of childbearing potential.

10.2 Substudy 1 Introduction

Substudy 1 will evaluate the safety, PK, PD, and preliminary efficacy of AZD8853 monotherapy in participants with selected advanced/metastatic solid tumours and aims to define MTD/RP2D. For an overview of Substudy 1 design, see Figure 3.

10.3 Substudy 1 Objectives and Endpoints

Refer to Section 3 for the master objectives and endpoints applicable to all Substudies in the study. Details of Substudy-specific objectives and endpoints are provided in Table 15.

Table 15 Substudy 1 Objectives and Endpoints

Type	Objectives	Endpoints
Secondary		
PD	To evaluate the PD activity of AZD8853 by assessment of candidate biomarkers in participants with selected advanced/metastatic solid tumours (Part A and Part B only)	• Change in circulating GDF15 serum levels
PD	To evaluate the intra-tumoural PD activity of AZD8853 in participants with selected advanced/metastatic solid tumours (Part B only)	• Change in CD8 tumour infiltration by IHC using baseline and on-treatment samples
Exploratory		
CCI	CCI	• CCI
CCI	CCI	• CCI
CCI	CCI	• CCI
CCI	CCI	• CCI

Type	Objectives	Endpoints
CCI	CCI	• CCI
CCI	CCI	• CCI

Abbreviations: BMI = body mass index; CCI GDF15 = Growth Differentiation Factor 15; IHC = immunohistochemistry; CCI ; PD = pharmacodynamics; PK = pharmacokinetic(s); SMI = skeletal muscle index.

10.4 Substudy 1 Study Design

10.4.1 Substudy 1 Design

In this Substudy of the FTiH, open-label, multicentre study, AZD8853 will be evaluated as monotherapy for safety, PK, PD, and preliminary efficacy in participants with selected advanced/metastatic solid tumours defined as:

- Second or later line setting of unresectable, locally advanced (Stage III) or metastatic (Stage IV) NSCLC that have progressed on anti-PD-1/PD-L1 inhibitors with or without platinum-containing chemotherapy.
- Third or later line setting of Stage IV MSS-CRC that have progressed on prior standard of care treatment.
- Second or later line setting of Stage IV UC that have progressed on prior treatment with platinum and/or checkpoint inhibitors.

The tumour types included in this study were selected based on unmet clinical need and underlying tumour biology. In both the dose-escalation (Part A) and dose-expansion (Parts B and C) parts of the study, participants with selected advanced/metastatic solid tumours who have progressed or are refractory to at least one line of standard therapy will be enrolled. These populations are thought to represent an unmet clinical need as currently available treatment options provide limited benefit. Moreover, internal investigation has revealed that NSCLC, MSS-CRC, and UC participants exhibit significantly higher serum GDF15 levels when compared to aged matched controls, and that higher serum GDF15 is correlated with a reduced overall survival (Mehta et al, 2015; Arfsten et al, 2019; and Traeger et al, 2019).

Participants will be followed until either death, loss to follow-up, withdrawal of consent or end of study. This Substudy of the study will comprise of 3 main parts (Figure 3), as follows:

Part A: Dose Escalation

The dose-escalation part of the study may enrol up to 45 participants (assuming up to 5 dosing cohorts and 3-9 participants per cohort) with selected advanced/metastatic solid tumours (NSCLC, MSS-CRC and UC). AZD8853 will be administered as monotherapy at the selected dose by i.v. infusion on a Q3W schedule. All participants will be treated until progressive disease, unacceptable toxicity, or withdrawal of consent.

See Section 10.6.6.1 for the starting dose, dose escalation and stopping criteria.

Part B: PD/MoA Expansion

Dose levels that are deemed safe in Part A of the study and have shown preliminary evidence of circulating free GDF15 reduction can be expanded in this PD/MoA expansion part of the study which will enrol up to approximately 20 participants with NSCLC and 20 participants with MSS-CRC advanced/metastatic solid tumours into 2 dose expansions (Part B1 and Part B2; approximately 10 NSCLC and 10 MSS-CRC participants in each part).

See Section 10.6.7 for details on PD/MoA expansion.

Mandatory archival, pre- and on-treatment tumour biopsies, serum GDF15 samples, and other samples including PK for each participant will be required at pre-specified timepoints. Pre- and on-treatment CD8+ PET imaging will be performed to assess PD response. Up to 10 participants in Part B1 and up to 10 participants in Part B2 will be enrolled with evaluable data from paired biopsies. Data from Part A and Part B of this Substudy of the study will inform tumour types and dose levels most suitable to progress onto an efficacy expansion part. The RP2D will be defined based on an updated PK/PD and safety analysis using data generated from both Part A and Part B of the study.

Cluster of Differentiation (CD)8+ Positron Emission Tomography (PET) Imaging

In Part B of the study, selected sites will use CD8+ PET imaging in combination with mandatory paired biopsies to monitor changes in CD8 T cell infiltration following treatment, to evaluate the correlation between the CD8 immune infiltrate present by IHC of biopsies with in vivo CD8 T cell localization by PET imaging using a ^{89}Zirconium (Zr)-deferoxamine (Df)-crefmirlimab.

Selected sites will recruit approximately up to 20 participants combined in Parts B1 and B2, across MSS-CRC and NSCLC study participants. These selected sites should prioritize recruitment to the CD8+ PET cohort of Part B prior to enrolling to non-CD8+ PET slots.

For further details on the CD8+ PET imaging, refer to Appendix I.

Part C: Efficacy Expansion

The efficacy expansion parts of the study will enrol up to approximately 40 participants in each expansion (Part C1 and Part C2). Relevant participants from Part B will count towards Part C efficacy expansions. These expansions may open either in parallel or sequentially at the Sponsor's discretion.

See Section 10.6.7 for details on efficacy expansion.

Mandatory pre- and on-treatment serum GDF15 samples and other samples including PK will be required. Archival of FFPE tissue is mandatory for all participants. Fresh pre- and on-treatment biopsies at pre-specified timepoints are CCI in this part of the study.

10.4.2 Substudy 1 Justification for Dose

A starting dose of 300 mg is proposed for AZD8853. The selection of the dose was based on the observed toxicology data from the cynomolgus monkey and a population PK model.

The HNSTD in non-human primate was estimated to be CCI mg/kg following CCI weekly doses with no toxicity concerns. Following AZD8853 administration, 100% reduction in serum GDF15 was observed with no apparent toxicity in animals. No changes in immunophenotyping and cytokine amounts were seen in the cynomolgus toxicology study. The observed Cmax and $AUC_{(0\text{-}168)}$ at CCI mg/kg in cynomolgus monkey was CCI µg/mL and CCI µg*h/mL. Based on FDA Guidance for Industry: S9 Nonclinical Evaluation for anti-cancer Pharmaceuticals a starting dose was calculated. CCI of the HNSTD was CCI mg/m^2, or a human equivalent dose of CCI mg/kg. For a CCI kg patient, this would equate to a CCI mg dose. An additional safety margin of CCI-fold was applied to allow for a starting dose of 300 mg.

A population PK model was developed based on available PK and GDF15 data from cynomolgus monkeys. An allometric scaling, with an exponent of 0.85 for clearances and 1 for volume of distributions was applied to translate relevant PK parameters from animals to humans. A target turnover model was used to predict the percentage decrease in free GDF15 in serum (Lowe et al, 2009; Davda et al, 2010). At the proposed starting dose of 300 mg, the predicted Cmax and $AUC_{(0\text{-}168hr)}$ in human were CCI µg/mL and CCI µg*hr/mL. Therefore a CCI-fold safety margin on Cmax and CCI-fold safety margin on $AUC_{(0\text{-}168hr)}$ is predicted.

At the proposed starting dose of 300 mg the model predicted a reduction of GDF15 at Cmax and C_{trough} of [redacted]% and [redacted]% respectively. Doses of 1000 and 3000 mg are expected to reduce free GDF15 levels by [redacted]% and [redacted]%, respectively at C_{trough}. A dose of 3000 mg is expected to have [redacted]-fold safety margins on Cmax and [redacted]-fold safety margins on $AUC_{(0\text{-}168hr)}$. Although a relatively high suppression of GDF15 is expected at Cmax, the levels of GDF15 are expected to recover rapidly given the fast turnover of GDF15 in humans (3 hours [Xiong et al, 2017], or 24 minutes from cynomolgus monkeys). In addition, AZD8853 is not a T cell agonist or an innate immune agonist and GDF15 suppression is not expected to cause cascading immune-stimulatory effects. A cytokine release assay was not conducted as GDF15 is a soluble factor and is not expected to cause cross-linking of immune cells. No changes in immunophenotyping or cytokine analysis were seen during the 3-month cynomolgus toxicology study [Three Month Intravenous Toxicity Study Two Month Assessment of Recovery in the Cynomolgus Monkey (8447292)].

Overall given that AZD8853 has a clear safety profile in toxicological studies, relatively high safety margins based on both absolute dose and predicted human exposure and is not expected to cause cascading immune-stimulatory effects, a 300 mg dose is proposed as a first-in-human dose.

10.4.3 End of Substudy 1 Definition

The end of Substudy 1 is defined as the last scheduled visit or contact of the last participant enrolled in the Substudy.

10.5 Substudy 1 Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Main Consent

Informed consent must be obtained prior to any study specific assessments. After the participant signs the ICF, a participant enrolment number will be assigned.

Based on study design as outlined in Section 10.4.1, participants will be enrolled in the study.

The main ICF for participants in this Substudy will include consent (mandatory and optional) for all biomarker samples as outlined in the SoA (Table 12, Table 13, and Table 14).

10.5.1 Substudy 1 Inclusion Criteria

In addition to the master study inclusion criteria listed in Section 5.1, participants are eligible to be included in this Substudy only if the further Substudy 1 criteria below also apply:

1 Histologically or cytologically documented unresectable, locally advanced (Stage III) or metastatic (Stage IV) NSCLC, metastatic (Stage IV) MSS-CRC or metastatic (Stage IV) UC.

2 Participants must meet all of the tumour-specific criteria below, with documented progression from previous therapy at study entry. Interval progression between 2 lines of therapy defines separate lines of therapy. Both standard and investigational treatments will count as lines of therapy when determining eligibility.

(a) Participants with NSCLC must:

i. Have received at least one prior line of systemic therapy in the advanced/metastatic setting.

ii. Have received at least one prior line of therapy which contained an anti-PD-1/PD-L1 agent, with or without platinum-based chemotherapy.

iii. Have documented test results for:

- Sensitizing EGFR mutations and ALK fusions/rearrangements
- Other genomic alterations which are part of a local standard of care and for which a locally approved standard of care targeted therapy exists (such as ROS proto-oncogene 1 [ROS1] fusions/rearrangements, neurotrophic receptor tyrosine kinase (NTRK) fusions, RET fusions/rearrangements, MET exon 14 skipping mutations, BRAF V600E mutation, etc.).

iv. Have received targeted therapy according to the identified genomic alteration. Targeted therapy is not mandatory if it is not in the local standard of care, or if it is refused by the participant or contraindicated.

v. <u>For Parts B and C: PD/MoA and Efficacy Expansions:</u>

No sensitizing EGFR mutations or ALK fusions/rearrangements (documented test result is mandatory).

(b) Participants with MSS-CRC:

i. Must have documented MSS by local testing (genetic analysis or immunohistochemistry).

ii. Must have received at least 2 prior lines of systemic therapy for advanced/metastatic disease.

- Prior systemic therapies must include fluoropyrimidines, irinotecan and oxaliplatin, unless refused or contraindicated. Participants may or may not have received a vascular endothelial growth factor (VEGF) agent (eg, bevacizumab), a BRAF inhibitor and an EGFR therapy (eg, cetuximab or panitumumab), according to local standard or care.

iii. Participants who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will be eligible to enter the study.

iv. Participants who had received adjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior line of chemotherapy.

(c) Participants with UC must:

i. Have histological confirmation of unresectable, locally advanced or metastatic UC (including any of the following: renal pelvis, ureters, urinary bladder, and/or urethra). Histological confirmation at initial diagnosis is acceptable. Participants must have received at least one prior line of systemic therapy including prior platinum-containing regimen and/or a checkpoint inhibitor therapy with anti-PD-1 or anti-PD-L1.

3 Participation in a clinical trial is determined to be the best option for next treatment based on prior response and/ or tolerability to standard of care in the opinion of the Investigator.

4 Participants must provide archival tumour tissue (FFPE block or unstained slides if a block cannot be provisioned). Refer to Section 10.8.6.2 and the Laboratory Manual for additional details.

Part B only:

5 All participants must be willing to provide mandatory paired biopsies (pre and on-treatment biopsies). The biopsied lesion must be distinct from any lesion used in the RECIST v1.1 evaluation.

6 CD8+ PET Cohort Only: Participants must have at least one non-liver lesion, suitable for PET imaging and be willing to be assessed with CD8+ PET imaging at screening (pre-treatment) and designated on treatment timepoints.

10.5.2 Substudy 1 Exclusion Criteria

In addition to the master study exclusion criteria listed in Section 5.2, participants are excluded from this Substudy if any of the further Substudy 1 criteria below also apply:

1. Participants who have received prior immunotherapy with anti-PD-1, anti-PD-L1, or anti-CTLA-4:
   a) Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.
   b) All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.
   c) Must not have experienced a ≥ Grade 3 imAE or a neurologic or ocular imAE of any grade while receiving prior immunotherapy. Note: Participants with an endocrine AE of ≤ Grade 2 are permitted to enrol if they are stably maintained on appropriate replacement therapy and are asymptomatic.

d) Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.

2. Participants with spinal cord compression or history of leptomeningeal carcinomatosis.
3. Participants with brain metastases unless treated, asymptomatic, stable, and not requiring continuous corticosteroids at a dose of > 10 mg prednisone/day or equivalent for at least 4 weeks prior to the start of the study.
4. CCI):
   Exclusion criteria for participation in the CCI component of the study include:
   a) CCI .
   b) CCI
   CCI .

10.6 Substudy 1 Study Intervention

10.6.1 Study Intervention(s) Administered

10.6.1.1 Investigational Products

Please refer to Section 6.1 for AZD8853 details.

10.6.1.2 Investigational Imaging Agent

Imaging sites will be provided with an investigational imaging agent (Part B only), an anti-CD8 minibody (Mb) (Crefmirlimab) conjugated with Df and radiolabelled with Zr-89 (^{89}Zr-Df-crefmirlimab), for participants in the CD8+ PET imaging cohorts (see Appendix I for more details).

10.6.2 Preparation/Handling/Storage/Accountability

Please refer to Section 6.2 for details on preparation/handling/storage/accountability of study intervention.

10.6.3 Measures to Minimise Bias: Randomization and Blinding

Please refer to Section 6.3 for details on randomisation and blinding.

10.6.4 Study Intervention Compliance

Please refer to Section 6.4 for details on study intervention compliance.

10.6.5 Concomitant Therapy

Please refer to Section 6.5 for details on concomitant therapy.

10.6.6 Dose Modification

Discontinuation or withholding of study intervention will be implemented to manage potential immune-related and non-immune mediated AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. Dose reductions are not permitted. For any ≥ Grade 3 AE that does not meet criteria for treatment discontinuation and whose causal relationship is attributable to the IMP, a single scheduled dose of IMP may be skipped (maximum of 2 non-consecutive doses) to permit resolution and the next dose will be administered on the next scheduled date. Omitted doses will not be administered at a later date. If the toxicity does not resolve to ≤ Grade 1 or baseline by the time of the next scheduled dose after skipping one dose of IMP (ie, a total of 2 consecutive doses are skipped), the participant will be permanently discontinued from treatment.

Potential risks for AZD8853 are expected to be similar to those of other human monoclonal immunoglobulins, and include immune-mediated and non-immune-mediated risks. The overall dose modifications, are given below:

- Grade 1 No dose modification.
- Grade 2 Hold study intervention until resolution to Grade ≤ 1 or baseline.
  - If toxicity worsens, then treat as Grade 3 or Grade 4.
  - Study intervention can be resumed once event stabilises to Grade ≤ 1.
  - Consider whether study intervention should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade < 1 upon treatment.
- Grade 3 Hold study intervention (see rules for Grade 2 events), or permanently discontinue as per AZD8853 TMG.
- Grade 4 Permanently discontinue study intervention.

For detailed guidelines on management of toxicities and dose modifications (temporary or permanent discontinuation only) refer to AZD8853 TMGs provided to the sites as a separate document.

10.6.6.1 Starting Dose, Dose Escalation Scheme and Stopping Criteria

10.6.6.1.1 Starting Dose

The initial dose level of 300 mg is based upon findings from the 3-month GLP toxicology study in cynomolgus monkeys and predictions around GDF15 suppression (see Section 10.4.2). The first participant in Cohort 1 must complete 1 week on study post the AZD8853 administration (Cycle 1 Day 1) without any DLTs before additional participants may be enrolled into the first cohort. A waiting period between additional participants in the cohort is not required.

10.6.6.1.2 Safety Review Committee

Please refer to Section 9.6 for details on the SRC.

10.6.6.1.3 Escalation Cohorts

Dose escalation will follow the mTPI-2 algorithm (Guo et al, 2017) as described below. Dose escalation cohorts will initially enrol 3 to 5 participants per cohort (to ensure at least 3 evaluable participants for dose-escalation decisions). A minimum of 3 participants must complete the DLT-evaluation period before making an escalation decision. A maximum of 9 participants may be enrolled in each dose-escalation cohort.

1. The MTD will be determined based on assessment of DLT according to the mTPI-2 algorithm (see Table 16).
2. A minimum of 3 DLT-evaluable participants are required in each dose level unless unacceptable toxicity is encountered in the first 2 participants prior to enrolment of the third participant, which would require dose de-escalation per the mTPI-2 design. For a dose level that has fewer than 3 participants who are DLT-evaluable, participants will be replaced.
3. If a de-escalation decision is made, choice of de-escalation to the previous main dose level or an intermediate dose level below will be at the discretion of the SRC. In the eventuality that a decision is made to de-escalate back to a dose escalation level that was previously deemed safe, in which additional participants (Part B1) have since been enrolled at that dose level, these participants will now be included in further dose-escalation decisions following mTPI-2 rules.
4. If a stay ("S") decision is made, additional participants will be enrolled up to a maximum of 9 participants for a given dose level (typically in groups of 2 to 4 participants).
5. After the sentinel dosing of the first participant in the initial cohort, participants 2 and 3 dosing will be staggered such that administration of the first dose is separated by at least 48-hours before the next participant is dosed. In subsequent cohorts, a 48-hour separation in first dosing between participants is required for the first 3 participants in each cohort. Provided there are no serious or unexplained safety issues after the first 3 participants, as determined by the respective treating physician, participants may be enrolled concurrently or sequentially for the remainder of the cohort with the Sponsor's agreement. Intra-participant dose escalation will not be allowed.
6. At the discretion of the Sponsor, dose escalation may be stopped before an MTD is reached. In this case, the doses for evaluation in the dose-expansion parts (Part B and Part C) may be chosen based on an assessment of available PK, PD, safety, or efficacy data.
7. The MTD will be determined by isotonic regression analysis applied to DLT rates observed during dose escalation using the mTPI-2 method (Guo et al, 2017).

The mTPI-2 employs a simple beta-binomial Bayesian model. Decision rules are based on calculating the UPM of three intervals corresponding to underdosing, proper dosing, and overdosing in terms of toxicity. The underdosing interval corresponds to a dose escalation, overdosing interval corresponds to a dose de-escalation, and proper dosing interval corresponds to staying at the current dose. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI-2 design calculates the UPMs for the multiple equal toxicity intervals, and the one with the largest UPM implies the corresponding dose-finding decision. The design for the dose-escalation part of the Substudy 1 uses a target DLT rate of CCI% and an equivalence interval of (CCI%, CCI%) for dose-escalation/de-escalation decisions as well as MTD determination. A dose level will be considered unsafe, with no additional participants enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of CCI% (ie, P [DLT > CCI% data] > 95%) with at least 3 DLT-evaluable participants treated and evaluated at that dose level. In Table 16 dose escalation/de-escalation decision rules are computed based on the above information.

Dose-escalation decisions guided by the mTPI-2 design with the targeted DLT rate p_T=CCI and the equivalence interval (EI) = (CCI). The table lists the decisions for up to 9 participants treated at a given dose. The column in this table represents the number of participants enrolled at the dose, and the row represents the number of DLTs at the same dose. The dose-escalation decisions are as follows: E: Escalate to the next higher dose; S: Stay at the current dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and marking the current dose and its higher doses as unacceptably toxic so that they will never be used again in the remainder of the trial.

10.6.7 Dose Expansion

Part B

The 2 dose expansion levels will be chosen based on peripheral target engagement and non-overlapping PK in order to evaluate intra-tumoural PD activity and help determine the RP2D. One dose expansion level will be the MTD/HPDD and one dose expansion level will be lower than the MTD/HPDD. Each dose level will enrol approximately 20 participants with NSCLC or MSS-CRC (enrolling approximately 10 participants in each tumour type). Expansions may open either in parallel or sequentially at Sponsor's discretion. Expansions may start before the MTD/HPDD has been determined.

Part C

The two efficacy expansions will be determined based on emerging data from Part A and/or Part B and may include two indications at a single dose level or one indication at two dose levels. If the RP2D cannot be adequately determined from Part B and additional data (eg, efficacy) is required to guide RP2D determination, then two dose levels in one indication will be investigated. If the RP2D is determined at the end of Part B, RP2D will be evaluated in two indications. Each efficacy expansion will enrol up to approximately 40 participants which may include up to 10 participants from the relevant Part B expansion. An interim analysis will take place after 20 participants (further details in Section 10.9.5).

10.6.7.1 Treatment Allocation in Dose Expansion Phase

Participants will not be randomised in this study; however, IxRS will be used in all parts of the study to ensure participants receive their allocated medication.

10.6.8 Definition of DLT

Dose limiting toxicity includes event(s) which happen during the 21 days of Cycle 1 of Part A and represent ≥ Grade 3 toxicity, as defined below, which is not clearly attributable to the disease under investigation, other concomitant medications, disease-related processes under investigation, or another non-drug-related aetiology, with modifications or exceptions noted below.

The DLT evaluation period is from the first exposure of AZD8853 until the end of Cycle 1, which is 21 days. All DLTs must be documented as AEs, graded according to

NCI CTCAE v5.0 and need to be followed until improvement to CTCAE Grade < 1. A minimum of at least 3 DLT-evaluable participants are required for the SRC to hold a dose-escalation vote.

An AE not listed below, or an AE meeting the DLT criteria below but occurring outside of the DLT period may be defined as a DLT-like event after consultation with the Sponsor and Investigators based on the emerging safety profile.

The following toxicities constitute a DLT:

- Any death not clearly due to the underlying disease or extraneous causes.
- Grade 4 adverse events of immune nature (imAE).
- Any ≥ Grade 3 non-infectious pneumonitis regardless of duration; diagnosis should include clinical evaluation, monitoring of oxygenation using pulse oximetry (resting and exertion), laboratory workup and high-resolution CT scan.
- Any ≥ Grade 3 non-infectious colitis irrespective of duration after confirmation by colonoscopy and histopathology.
- Any Grade 3 imAE, including rash, pruritus, or diarrhoea (NOTE: this excludes colitis or pneumonitis, as these AEs are already defined above), that does not downgrade to Grade ≤ 2 within 7 days after onset of the event despite maximal supportive care including systemic corticosteroids.
- Liver transaminase elevation:
    i. Criteria for all participants except participants with elevated transaminases (ALT/AST) at baseline/screening due to liver metastasis:
        - Isolated liver transaminase elevation > 5 × but ≤ 8 × ULN that does not downgrade to AST/ALT ≤ 3 x ULN within 14 days after onset with optimal medical management.
        - Isolated liver transaminase elevation > 8 × ULN regardless of duration or reversibility.
        - Any increase in AST or ALT > 3 × ULN and concurrent increase in TBL ≥ 2 × ULN, regardless of duration or reversibility, where no other reason, other than the study intervention, can be found to explain the combination of increases.
    ii. Criteria for participants with elevated transaminases (ALT/AST) at baseline/screening due to liver metastasis (inclusion criterion 8):
        - Isolated liver transaminase elevation > 2 × but ≤ 5 × baseline that does not downgrade to < 2 × baseline or less within 14 days after onset with optimal medical management.

  - Isolated liver transaminase elevation > 5 × baseline regardless of duration or reversibility.
  - Any increase in AST or ALT > 3 × baseline and concurrent increase in TBL ≥ 2 × ULN regardless of duration or reversibility, where no other reason, other than the study intervention, can be found to explain the combination of increases.

- Grade 3 nausea, vomiting, or diarrhoea that does not resolve to Grade ≤ 1 within 3 days of initiation of maximal supportive care.
- Neutropenia:
  i. ≥ Grade 3 febrile neutropenia regardless of duration ruling out the cause of fever due to non-infections events.
  ii. ≥ Grade 3 neutropenia, without associated fever or systemic infection, which does not improve by at least one grade within 5 days of onset.
- Anaemia:
  i. Grade 4 anaemia regardless of duration.
  ii. Grade 3 anaemia that requires more than one transfusion of > 2 units of red blood cell.
- Thrombocytopenia:
  i. ≥ Grade 4 thrombocytopenia lasting > 7 days.
  ii. ≥ Grade 3 thrombocytopenia, regardless of duration, associated with haemorrhage.
- Thrombocytopenia in presence of anticoagulation therapy:
  i. Thrombocytopenia below Grade 3 lasting for 7 days, without additional risk factors.
- Any ≥ Grade 3 neurotoxicity (to include but not limited to limbic encephalitis, autonomic neuropathy, including peripheral neuromotor syndromes such as myasthenia gravis and Guillain-Barré) regardless of duration.
- Any ≥ Grade 3 cardiotoxicity (to include but not limited to arrhythmias, myocarditis with cardiomyopathy, ventricular dysfunction) regardless of duration.
- Any ≥ Grade 3 ocular toxicity (including but not limited to iritis, uveitis, significant vision changes) regardless of duration.
- Any other pre-existing toxicity that has worsened as compared to baseline that is clinically significant and unacceptable, does not respond to supportive care, results in a disruption of dosing schedule of more than 21 days or is judged to be a DLT by the SRC.

The DLT definition excludes the following conditions:

- Grade ≥ 3 fatigue lasting ≤ 7 days.
- Concurrent vitiligo or alopecia of any grade.
- Grade 3 or Grade 4 lymphopenia, unless associated with infection.
- Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis, irrespective of duration.
- Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.

10.6.9 Definition of maximum tolerated dose

The MTD will be selected from all tried dose levels that have not been previously declared to be unsafe with a DU decision according to the mTPI-2 decision table. With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of CCI %.

In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of CCI %, the following approach will be used (Ji et al, 2010): among all tied dose levels the highest dose level with target toxicity CCI % will be selected, unless all tied dose levels have estimated toxicity CCI %, in which case the lowest dose level will be selected.

10.6.10 Definition of DLT Evaluable Participant

For decisions on dose escalation, an evaluable participant is defined as a participant who has received AZD8853 and either:

- Has received at least 75% of the AZD8853 infusion and has completed safety evaluation requirements during the DLT evaluation period of 21 days in Cycle 1. Participants who do not remain in the study up to this time for reasons other than DLT will be considered non-evaluable for DLT assessment.

OR

- Has experienced a DLT during the DLT evaluation period.

Non-evaluable participants in the dose-escalation cohorts will be replaced in the same dose cohort if needed to ensure a minimum of 3 DLT-evaluable participants.

10.6.11 Intervention after the End of the Study

Please refer to Section 6.7 for details on intervention after the end of the study.

10.7 Substudy 1 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

10.7.1 Discontinuation of Study Intervention

Please refer to Section 7.1 for details on discontinuation of study intervention.

10.7.2 Participant Withdrawal from the Study

Any participant in Part A that is withdrawn and is not evaluable will be replaced to ensure a minimum number of 3 DLT-evaluable participants.

10.7.3 Lost to Follow-up

Please refer to Section 7.3 for lost to follow-up.

10.8 Substudy 1 Study Assessments and Procedures

In addition to the master study assessment and procedures listed in Section 8, the below Substudy specific assessments and procedures also apply.

- Approximately 86 mL of blood will be required for all screening tests which will be conducted during the 28-day screening period. Approximately 210 mL of blood (including CCI [redacted]) will be collected between Days 1 and 21 of study intervention in Part A and Part B whereas during the same time period approximately 189 mL of blood (including CCI [redacted]) will be collected in Part C. No more than approximately 144 mL of blood will be drawn during any cycle or individual study visit after Cycle 1. The total volume to be collected will depend on the number of doses administered and the length of follow-up.
- All efficacy assessments should continue until progression; however, if the participant is clinically stable then a confirmatory scan for progression could be performed per Investigator's discretion, and assessments should also be performed when a participant's study intervention has been stopped.

10.8.1 Efficacy Assessments

Please refer to Section 8.1 for the efficacy assessments

10.8.2 Safety Assessments

Details of all safety assessments are provided in Section 8.2, for the planned timepoints for the safety assessments refer to SoA (Table 12, Table 13, and Table 14).

10.8.2.1 Electrocardiograms

Please refer to Section 8.2.4 for details of ECGs. Table 17 provides the Substudy-specific sampling schedule of electrocardiograms.

Table 17 Sampling Schedule for Electrocardiograms

Cycle	Day	Sampling Time	Sampling Window
Parts A, B and C			
1	1	Pre-dose	-2 hrs
	1	0 hrs post EoI	+15 min
2	1	Pre-dose	-2 hrs
3	1	Pre-dose	-2 hrs
7-n	1	Pre-dose Q12W	-2 hrs
EOT	N/A	Up to 14 days post EOT	

Abbreviation: EoI = end of infusion; EOT =end of treatment; hrs = hours; min = minutes; N/A = not applicable

10.8.3 Adverse Events and Serious Adverse Events

For details on AEs and SAEs, refer to Section 8.3.

10.8.4 Overdose

Please refer to Section 8.4 for details on overdose.

10.8.5 Human Biological Samples

10.8.5.1 Pharmacokinetics

Please refer to Section 8.5.1 for details of PK. Table 18 provides the Substudy-specific sampling schedule for the PK samples.

Table 18 Sampling Schedule for PK Samples

Cycle	Day	Sampling Time	Sampling PK Window
Part A			
1	1	Pre-dose	-2 hrs
	1	0 hrs post EoI	+5 min
	1	15 min post EoI	±5 min
	1	2 hrs post EoI	±5 min
	1	6 hrs post EoI	±5 min
	2	24 hrs post EoI	±5 min
	8	168 hrs post EoI	±5 min
	15	336 hrs post EoI	±5 min
2, 3, 4, 5, and 6	1	Pre-dose	-2 hrs
2, 3, 4, 5, and 6	1	0 hrs post EoI	+5 min
2[a]	8	168 hrs post EoI	±5 min

Cycle	Day	Sampling Time	Sampling PK Window
EOT	N/A	90 days post EOT	±7 days
Part B			
1	1	Pre-dose	-2 hrs
	1	0 hrs post EoI	+5 min
	1	15 min post EoI	±5 min
	1	2 hrs post EoI	±5 min
	1	6 hrs post EoI	±5 min
	2	24 hrs post EoI	±5 min
	8	168 hrs post EoI	±5 min
	15	336 hrs post EoI	±5 min
2,3,4,5, and 6	1	Pre-dose	-2 hrs
EOT	N/A	90 days post EOT	±7 days
Part C			
1	1	Pre-dose	-2 hrs
	1	0 hrs post EoI	+5 min
2,3,4,5, and 6	1	Pre-dose	-2 hrs
EOT	N/A	90 days post EOT	±7 days

[a] Taken at time of second paired biopsy
Abbreviation: EoI = end of infusion; EOT = end of treatment; hrs = hours; min = minutes; N/A = not applicable

10.8.5.2 Immunogenicity Assessments

Please refer to Section 8.5.2 for details of immunogenicity assessments. Table 19 provides the Substudy-specific sampling schedule for the ADA samples.

Table 19 Sampling Schedule for ADA Samples

Cycle	Day	Sampling Time	Sampling ADA Window
Parts A, B and C			
1	1	Pre-dose	-2 hrs
2	1	Pre-dose	-2 hrs
3	1	Pre-dose	-2 hrs
5	1	Pre-dose	-2 hrs
7-n	1	Pre-dose Q12W	-2 hrs
EOT	N/A	Up to 14 days post EOT	
EOT	N/A	30 days post EOT	±7 days
EOT	N/A	90 days post EOT	±7 days

Abbreviation: EOT = end of treatment; hrs = hours; N/A = not applicable; Q12W = every 12 weeks

10.8.5.3 Pharmacodynamics

Blood samples will be collected at specific timepoints mentioned in the SoA (Table 12, Table 13, and Table 14).

Further details on sample processing, handling and shipment will be provided in the Laboratory Manual.

For storage, re-use, and destruction of pharmacodynamic samples see Appendix C.

10.8.5.3.1 GDF15 Assay for Target Engagement

As specified in the SoA for study visits (Table 12 and Table 13) and per the additional timepoints denoted in Table 20, samples for determination of free GDF15 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the method to be used will be described in a separate bioanalytical report.

Table 20 Sampling Schedule for GDF15 Target Engagement Samples

Cycle	Day	Sampling Time	Sampling PD Window
1	1	Pre-dose	-2 hrs
	1	0 hrs post EoI	+5 min
	1	15 min post EoI	±5 min
	1	2 hrs post EoI	±5 min
	1	6 hrs post EoI	±5 min
	2	24 hrs post EoI	±5 min
	8	168 hrs post EoI	±5 min
	15	336 hrs post EoI	±5 min
2, 3, 4, 5, and 6	1	Pre-dose	-2 hrs
2, 3, 4, 5, and 6	1	0 hrs post EoI	+5 min
2[a]	8	168 hrs post EoI	±5 min
EOT	N/A	Up to 14 days post EOT	
EOT	N/A	30 days post EOT	±7 days
EOT	N/A	90 days post EOT	±7 days

[a] Taken at time of second paired biopsy
Abbreviations: EoI = end of infusion; EOT = end of treatment; hrs = hours; min = minutes; N/A = not applicable

10.8.6 CCI [redacted]

10.8.6.1 Fresh Tumour Biopsy

Fresh tumour biopsy samples (both mandatory and CCI [redacted]) will be collected for participants enrolled in both the dose-escalation part (Part A) and the expansion parts (Part B and Part C). For mandatory and CCI [redacted] biopsy participants, the associated pathology report(s) for fresh tumour samples will be required at screening and requested on-treatment for all participants enrolled into the study (details in the Laboratory Manual). If clinically feasible, at each fresh tumour sample timepoint, participants will undergo 4 core image-guided needle biopsies. Details for fresh tumour sample collection, processing, storage, and shipment are provided in the Laboratory Manual. Per institutional practice, image-guided fresh core needle tumour biopsies should be preferentially obtained from tumour tissues that are safely accessible, as determined by the Investigator, and are not obtained from sites that require significant risk procedures. Collection of tumour cells from fluid such as ascites or pleural effusion is not permitted. Fine-needle aspirate specimens are not acceptable. For fresh tumour biopsies, the tumour lesion should not be used as a RECIST target lesion, unless this is the only soft tissue lesion. If a RECIST v1.1 TL is used for biopsy, the lesion must be ≥ 2 cm in the longest diameter and must be biopsied at least 2 weeks prior to baseline RECIST assessment. Sites should confirm adequacy of tumour biopsy material at the time of the procedure. The screening and on-treatment biopsy should be taken where possible from the same lesion to ensure consistency and reduce variability of the sample. Biopsies should not be taken from previously irradiated sites unless the lesions were progressing after radiation. Bone biopsies are not permitted.

All tumour biopsies will be collected, stored, and shipped as detailed in the Laboratory Manual.

10.8.6.1.1 Mandatory Fresh Paired Biopsies

Up to 40 participants in Part B will be required to provide tumour samples. These participants will be required (mandatory) to undergo a tumour biopsy pre-treatment and during treatment as described below.

- Cycle 1 Day 1 (≤ 14 days, must be before the initial dosing of study intervention)
- Cycle 2 Day 8 (± 5 days, must be after CD8+ PET imaging if participant is in the CD8+ PET cohort).
- Informed consent must be obtained from any participant who agrees to provide tissue for mandatory tumour tissue sample testing.

10.8.6.1.2 CCI [redacted]

CCI [redacted] . CCI [redacted]

CCI

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10.8.6.1.3 CCI

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10.8.6.2 Mandatory Archival Tumour Samples

Sites must provision archival tumour tissue (FFPE blocks), with sufficient material to produce approximately 40 slides. Provision of archival FFPE blocks is preferred, but if an archival block is not available, then approximately 40 unstained slides must be provided from another biopsy. Associated pathology report(s) for biopsy samples must be provided at screening for all participants. Central confirmation of the number of slides available is not required prior to participant dosing. However, sites should ensure that the archival block or other tissue sample has sufficient material, to the best of their knowledge, to produce the required number of slides. In the event that less than approximately 40 sections are thought to be available, then the CRA or Sponsor representative should be contacted. Please refer to the Laboratory Manual for details of acceptable sample types, processing, storage, and shipment of tissue samples.

10.8.6.3 CCI

CCI

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CCI

CCI

CCI

CCI

CCI [redacted]

10.8.6.4 CCI [redacted]

Whole blood samples will be collected from all participants as described in the SoA, for preparation of CCI [redacted] and are mandatory. A variety of assays include, but are not limited to, CCI [redacted]

10.8.6.5 Whole Blood for Flow Cytometry

Whole blood samples will be collected from all participants as described in the SoA, for flow cytometry-based immunophenotyping of circulating lymphocytes and are mandatory. Populations to be assessed may include, but are not limited to: T cell subsets, B cell subsets, natural killer cells, DCs, and myeloid-derived suppressor cells. Markers will also be used to investigate the expression of immune checkpoint molecules and activation and proliferation status of immune cells.

10.8.6.6 Circulating Tumour DNA

Whole blood to extract plasma will be collected from all participants as described in the SoA, for, but not limited to, ctDNA analysis and is mandatory. The ctDNA samples will be analysed longitudinally for secondary and CCI [redacted], and to CCI [redacted] in CCI [redacted] and CCI [redacted].

10.8.6.7 Whole Blood for CCI [redacted]

Whole blood to extract CCI [redacted] will be collected from all participants as described in the SoA, for analysis of CCI [redacted] and is mandatory. CCI [redacted]

CCI [redacted]

10.8.6.8 CCI [redacted] Research

Already collected samples may be analysed on CCI [redacted] thought to play a role in CCI [redacted] to AZD8853.

For storage, re-use and destruction of biomarker samples see Section 8.5 and Appendix C.

10.8.6.9 CCI Future Scientific Research

Already collected samples may be analysed to support research beyond AZD8853 and is pursuant to agreement to a separate CCI for future scientific research. Future research is important to advance science and public health. At present, however, it is not possible to foresee all details of future scientific research projects. These future scientific research projects are beyond the scope of the clinical study.

10.8.7 CCI

Please refer to Master Protocol Section 8.7 for details on the CCI

10.8.8 Health Economics and Participant eConsent Opinions

Please refer to Section 8.8.

10.9 Substudy 1 Statistical Considerations

Statistical considerations as described in Section 9 will be followed in the analysis of Substudy 1, unless specifically stated in this section. Substudy-specific considerations are described in this section.

10.9.1 Statistical Hypotheses

Not applicable.

10.9.2 Sample Size Determination

For dose escalation (Part A) cohorts of 3 to 9 evaluable participants will be enrolled. The total number of participants will depend on the number of non-evaluable participants and the number of dose escalations necessary in order to declare MTD/RP2D. It is anticipated that approximately up to 5 dose-escalation cohorts of up to 9 evaluable participants may be included resulting in an overall total of up to approximately 45 participants.

Dose escalation using mTPI-2 is visualised in Table 16.

In the PD/MoA expansions (Part B1 and B2) up to 10 participants may be enrolled in each of 2 dose levels and 2 indications (NSCLC and MSS-CRC) for a total of approximately 40 participants. It is estimated that this will provide at least 7 participants per indication and dose level with evaluable paired biopsies for PD assessment.

In the efficacy expansions (Part C1 and C2) up to 40 participants in each expansion will be enrolled for a total of 80 participants. This will be an additional 30 participants per expansion since 10 relevant participants may be included from the associated PD/MoA expansion. With

CCI [redacted] Clopper et al, 1934) CCI [redacted]

Across all parts of the study up to a total of 165 participants may be enrolled and treated with AZD8853 (145 participants if 20 participants from Part B are included in Part C). Additional participants may be required if additional expansions or dosing schedules are explored.

10.9.3 Population for Analyses

In addition, to the populations for analyses mentioned in Section 9.3, the definition of Substudy 1 specific populations for analyses is provided in Table 21.

Table 21 Populations for Analyses

Population/Analysis set	Description	Endpoint/Output
PD	All participants who receive at least one dose of study intervention with baseline measurement and at least one reportable pharmacodynamic measurement.	PD endpoints

Abbreviation: PD = pharmacodynamics

10.9.4 Statistical Analyses

10.9.4.1 General Considerations

Data will be presented by dose cohort (Part A) and dose expansion (Part B and Part C); no direct statistical comparisons will be made between any cohorts or expansions.

Table 22 details which data will be analysed at each timepoint.

Table 22 Details of Analyses

Analysis	Trigger	Data Type Included
Interim for efficacy expansions (Parts C1 and C2)	After the 20th participant in each expansion had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from treatment	Efficacy Safety
Primary analysis	At completion of each part (analysis will be conducted separately for each part)	All data

10.9.4.2 Efficacy Analyses

Please refer to Section 9.4.3 for efficacy analyses.

10.9.4.3 Safety Analyses

Please refer to Section 9.4.2 for safety analyses.

10.9.4.4 Other Analyses

10.9.4.4.1 Pharmacodynamics

The secondary PD endpoint of change in circulating GDF15 serum levels from pre-treatment (baseline) to each post baseline timepoint as well as the maximum change will be summarised using descriptive statistics on actual and percent change.

The secondary endpoint of change in CD8 tumour infiltration by IHC between the pre-treatment and on-treatment biopsy will be summarised using descriptive statistics for those participants with paired biopsies.

In general, PD variables based on CCI and fresh biopsy samples will be summarized using descriptive statistics on the PD Population. Summaries of change from baseline and percent change from baseline will be also be presented for PD variables as appropriate. Such summaries may be reported separately from the main CSR. Summaries and analyses for CCI may be reported outside the CSR in a separate report. Descriptive statistics will be the primary method for the biomarker analyses. Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well.

Analyses of PK/PD may include, but are not limited to, CCI . Other CCI . Where relevant, data collected from this study may be combined with other data from other studies for modelling purposes. All analysis results may be reported separately from the CSR.

Refer to Section 9.4.4.1 for information on PK and immunogenicity analyses. Further details on the analysis of immunogenicity, pharmacokinetics and pharmacodynamics will be provided in the SAP.

10.9.5 Interim Analyses

In the efficacy expansions (Part C1 and Part C2) an interim analysis will be performed after the 20th participant in each expansion has had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from treatment. Enrolment will continue while this analysis is ongoing. The analysis will provide tolerability and safety data and will also provide a reasonable chance to determine if there is a lack of efficacy. CCI CCI

CCI [redacted]

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - i. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - ii. Applicable ICH GCP Guidelines
  - iii. Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Regulatory Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
  - Sites participating in the CD8+ PET imaging portion of the study will be provided with separate Part B ICFs.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

The ICF will contain a separate section that addresses and documents the collection and use of

any mandatory and/or optional human biological samples. The Investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from Regulatory Authorities.

A 5 Committees Structure

No Data Monitoring Committee will be used in this study; however, a SRC will closely monitor participant safety on an ongoing basis. The SRC Members will include the following:

- Principal Investigator, or delegate, who will chair the committee
- Study Chair (if not Principal Investigator)
- Principal Investigator or delegate from investigational site
- AstraZeneca Medical Science Director or delegate
- AstraZeneca Global Safety Physician, or delegate

The Sponsor or CRO Study Physician, or delegate, should always be present at the SRC.

The AstraZeneca Clinical Pharmacology Scientist, Study Statistician, Patient Safety Scientist, Study Leader and other AstraZeneca and non-AstraZeneca technical experts may also be invited as appropriate. The SRC Remit document for this study will define the exact membership and who will be present for decisions to be made.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and

http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CRO).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).
- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first site open and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the Regulatory Authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant 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.

B 2 Definitions of Serious Adverse Event

A serious adverse event is an AE occurring during any study period (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-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for **malignant tumours** reported during a study should generally be assessed as **serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the investigational medicinal product under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the participant 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 participant'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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

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 participant or may require medical treatment 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

Intensity Rating Scale:

The grading scales found in the revised NCI CTCAE v5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

B 3 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 participant 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 no available facts or arguments to suggest a causal relationship, 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.

B 4 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 drug that either causes harm to the participant or has the potential to cause harm to the participant.

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 participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- 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 participant received the medication (excluding IRT]/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTMS errors)

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

- Errors related to or resulting from IRT/RTMS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Participant 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 AstraZeneca product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The Investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

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 record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

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

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented, and study site notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

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. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

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, C, D, and E viruses. They are assigned the following UN number and proper shipping name

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

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D CCI [redacted]

D 1 CCI [redacted]

- AstraZeneca intends to collect and store CCI [redacted]
- CCI [redacted]
- The results of CCI [redacted] may be reported in a separate study summary.
- The Sponsor will store the CCI [redacted] in a secure storage space with adequate measures to protect confidentiality.

D 2 CCI [redacted] Plan and Procedures

Selection of CCI [redacted] Population

- All participants will be asked to participate in this CCI [redacted]. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this CCI [redacted], participants must fulfil all of the inclusion criteria described in the main body of the Master CSP and: Provide informed consent for the CCI [redacted] (refer to Section 5.1).

Exclusion Criteria

- Exclusion from this CCI [redacted] may be for any of the exclusion criteria specified in the main study (refer Section 5.2)

Withdrawal of Consent for CCI [redacted]

- Participants may withdraw from this CCI [redacted] at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the Master CSP.

Collection of Samples for [redacted]

- The blood sample for this [redacted] will be obtained from the participants at the visit specified in the relevant Substudy SoA. Although [redacted] is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at the planned visit, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for [redacted] during the study.

Coding and Storage of [redacted] **Samples**

- The processes adopted for the coding and storage of samples for [redacted] are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. [redacted] 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 sample either before or at the time of [redacted] extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca [redacted] 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 [redacted]).
- The link between the participant 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 [redacted] samples for analysis, facilitate correlation of [redacted] with clinical data, allow regulatory audit, and permit tracing of 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 [redacted] component, are outlined in Appendix A.

Informed Consent

- The [redacted] of this study is [redacted], and the participant may participate in other components of the main study without participating in this [redacted]. To participate in the [redacted] of the study the participant must sign and date both the consent form for the main study and the addendum for the [redacted] of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Principal Investigator(s) is

responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdrawal from the [redacted] of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual [redacted] results to participants, 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 [redacted] being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the [redacted] and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her [redacted]. Regulatory Authorities may require access to the relevant files, though the participant's medical information and the [redacted] would remain physically separate.

Data Management

- Any [redacted] generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as [redacted]) from this [redacted] with other researchers, such as hospitals, academic organisations 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 participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the [redacted] in a suitable secure environment separate from the clinical database.

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

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver anomalies can be found in the Dose Modification section of each Substudy in the CSP.

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

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including 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 AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

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

E 2 Definitions

Potential Hy's Law
Aspartate transaminase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
Aspartate transaminase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, 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.

E 3 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 participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local Laboratories Being Used:

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

- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not Met

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

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

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section E 6)
- Notify the AstraZeneca representative who will then inform the central Study Team

- Within one 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 participants 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 participant's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
    - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
    - Complete the three Liver eCRF Modules as information becomes available.

E 5 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 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 date PHL criteria was 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 AstraZeneca 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:

- Provides any further update to the previously submitted SAE of PHL, (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.

E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to participants with liver metastases who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met the Investigator will determine if there has been a **significant change** in the participants' condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required.

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2.

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study treatment and has already met PHL criteria at a previous on-study treatment visit (Section E 6).

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 described in Section E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the participant'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 described in Section E 4.2 for reporting PHL as an SAE

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) 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 Study Physician if there is any uncertainty.

E 8 Laboratory Tests

Local Laboratory Tests	
Additional standard chemistry and coagulation tests	Gamma-glutamyltransferase Lactate dehydrogenase Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV
	HEV RNA
Other viral infections	IgM & IgG anti-cytomegalovirus IgM & IgG anti-herpes simplex virus IgM & IgG anti- anti-Epstein-Barr virus
Alcoholic hepatitis	CD-transferrin [c]
Autoimmune hepatitis	ANA Anti-LKM ASMA
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

Abbreviations: ANA = antinuclear antibody; ASMA = anti-Smooth Muscle Ab; CD = carbohydrate deficient transferrin; DNA = deoxyribonucleic acid; HAV = hepatitis A virus; HBc = hepatitis B core; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalised ratio; LKM = Liver/Kidney Microsomal Ab; RNA = ribonucleic acid

E 9 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

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

Introduction

This appendix details the implementation of RECIST v1.1 guidelines (Eisenhauer et al, 2009). Investigator assessments will use the RECIST v1.1 guidelines described in this appendix.

Imaging modalities and acquisition specifications for RECIST v1.1

A summary of the imaging modalities that can be used for tumour assessment TLs, NTLs, and NLs is provided in Table 23.

Table 23 Summary of Imaging Modalities for Tumour Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) FDG-PET/CT

Abbreviations: CT = Computed tomography; FDG-PET/CT = ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI = Magnetic resonance imaging.

CT and MRI

Computed tomography with i.v. contrast is the preferred imaging modality (although MRI with i.v. contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumour assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc.), imaging facility, tumour assessor (eg, radiologist), and method of tumour assessment (eg, RECIST v1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumour assessment schedule as closely as possible (refer to the Schedules of Activities [SoAs; Table 12, Table 13, and Table 14]), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body

scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artifacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumour evaluation are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest-abdomen (-pelvis). Coverage 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 participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a NL representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up timepoints. This will enable better consistency not only of tumour measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumour burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these timepoints are specified in the SoAs (Table 12, Table 13, and Table 14). Examples include the following:

- Intravenous contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Non-contrast CT of chest and i.v. contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Intravenous contrast-enhanced CT or MRI of the head and neck
- Intravenous contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when participants have sensitivity to i.v. contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with i.v. CT contrast (most preferred)
2 Chest CT without i.v.-contrast + abdomen (-pelvis) MRI with i.v. MRI contrast, if CT i.v. contrast (iodine based) is medically contraindicated at any time during the study

3 Chest-abdomen (-pelvis) CT without i.v. contrast, if both i.v. CT and MRI contrast are medically contraindicated, or the participant has compromised renal function
4 Chest-abdomen (-pelvis) MRI with i.v. MRI contrast, if CT cannot be performed at any time during the study

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumours require consistent administration (dose and rate) of i.v. contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumour lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤ 5-mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-Ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Plain X-Ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

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 NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed

equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a progressive disease assessment at that timepoint.

FDG-PET/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/CT scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST v1.1 assessments according to the following algorithm: NLs will be recorded where there is positive FDG uptake[1] not present on baseline or prior FDG-PET/CT scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the FDG-PET/CT scan. The PET portion of the PET/CT introduces additional data that may bias an Investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET/CT scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST v1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with i.v. contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST v1.1 tumour assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound examination will not be used for RECIST v1.1 assessment of tumours as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumour size. Tumours identified by ultrasound

[1] A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed.

will need to be assessed by correlative CT or MRI anatomical scan.

Other Tumour Assessments

Clinical Examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST v1.1 assessments. Tumours identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Histology and Cytology

Histology or tumour markers on tumour biopsy samples will not be used as part of the tumour response assessment as per RECIST v1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumour response assessment as per RECIST v1.1.

Furthermore, an overall assessment of complete response (all other disease disappears/reverts to normal) would be changed to partial response if an effusion remains present radiologically.

Measurability of Tumour Lesions at Baseline

RECIST 1.1 Measurable Lesions at Baseline:

A tumour lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter for non-nodal lesions or ≥ 15 mm in short axis[2] diameter for lymph node lesions with i.v. contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST v1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable Lesions at Baseline:

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural effusion, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10-mm to < 15-mm short axis diameter at baseline[3])
- Previously irradiated lesions[4]
- Brain metastasis

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[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

[3] Lymph nodes with < 10-mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

[4] Localized post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

Special Considerations Regarding Lesion Measurability at Baseline:

- Bone lesions
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - 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 lesions thought to represent 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 participant, these should be selected over cystic lesions as TLs.

RECIST v1.1 TL Selection at Baseline:

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter 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 that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases for TL assessment at baseline:

- For TLs 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 diameter.

- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumour lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

RECIST 1.1 NTL Selection at Baseline:

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of Tumour Response and Progression

RECIST v1.1 TL Assessment at Follow-up

This section defines the criteria used to determine objective tumour visit response for RECIST v1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.

- 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 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of "Too large to measure" in the case report form will trigger an overall visit response of progressive disease.
- When a TL has had any intervention (eg, definitive radiotherapy, embolization, surgery, transarterial chemoembolization, etc.) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST v1.1 case report form for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 24 RECIST v1.1 Evaluation of Target Lesions

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to < 10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for progressive disease.
Progressive Disease	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir)—This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) 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 TL response.
NA	Only relevant if no TLs present at baseline.

Abbreviations: CR = complete response; NA = not applicable; NE = not evaluable; PR = partial response; SD = stable disease; TL = target lesion.

RECIST v1.1 NTL Assessment at Follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or

partial response in TLs, the overall tumour burden has increased sufficiently to merit unequivocal progression by NTLs. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Table 25 RECIST 1.1 Evaluation of Non-Target Lesions

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/non-progressive disease	Persistence of one or more NTLs.
Progression of disease	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For participants without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
NA	Only relevant if no NTLs present at baseline

Abbreviations: CR = Complete response; NA = Not applicable; NE = Not evaluable; NTL = Non-target lesion; TL = Target lesion.

RECIST v1.1 NL Identification at Follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the case report form. The presence of one or more NLs is assessed as progression. The finding of a NL 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 NL is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a NL and will indicate disease progression.

RECIST v1.1 Evaluation of Overall Visit Response at Follow-Up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 26.

Table 26 RECIST v1.1 Overall Visit Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-progressive disease	No	PR
CR	NE	No	PR
PR	Non-progressive disease or NE or NA	No	PR
SD	Non-progressive disease or NE or NA	No	SD
NA	Non-CR/Non-progressive disease	No	SD (non-CR/non-progressive disease)
NE	Non-progressive disease or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease

Abbreviation: CR = complete response; NA = not applicable; NE = not evaluable; NED = no evidence of diseases; PR = partial response; SD = stable disease; TL = target lesion.

[a] Non-CR/Non-progressive disease for Overall Response if only non-target lesions (no TLs) are present at baseline.

Note: An overall assessment of Complete Response (all other disease disappears/reverts to normal) would be changed to Partial Response if ascites remains present radiologically.

The following overall visit responses are possible depending on the extent of tumour disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, progression of disease, or NE
- For participants with NTLs only (at baseline): CR, Non-CR/Non-progressive disease, progressive disease, or NE
- For participants with no disease at baseline: no evidence of disease (available as an option in the electronic case report form), progressive disease, or NE

Evaluation of Scans Subsequent to RECIST v1.1-defined Progression

A follow-up scan is left up to the Investigator's discretion but, if performed, should be at least 4 weeks after a RECIST v1.1-defined radiological progression and no later than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the Investigator for patient management and further treatment decisions, and since the published RECIST v1.1 criteria (Eisenhauer et al, 2009) do not provide guidance on how to assess scans acquired after RECIST v1.1-defined progressive disease, supplemental instructions for Investigators on how to evaluate these follow-up scans are provided below. If the follow-up scan acquired after a RECIST v1.1 progressive disease scan meets *any* of the following criteria, it will be assigned an overall visit response of progressive disease, and if the scan does not meet *any* of these 4 criteria, the timepoint assessment will be non-progressive disease (ie, CR, PR, SD, or NE).

- ≥ 20% increase and at least a 5-mm increase in the sum diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥ 5 mm in the sum of diameters at the follow-up timepoint compared with the immediate prior timepoint
- significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint
- significant progression (worsening) of previously new lesions (pre-existing new lesions) at the follow-up scan timepoint compared with the immediate prior timepoint
- additional unequivocal brand-new lesions at the follow-up scan timepoint

Central Imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for quality control, storage, and potentially for BICR. Digital copies of all original scans should be stored at the Investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator tumour assessments will not be shared with the central reviewers. The management of participants will be based in part upon the results of the tumour assessments conducted by the Investigator. Further details of the BICR will be documented in an Independent Review Charter.

Appendix G Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the AstraZeneca Study Physician.

G 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections G 2 to G 5. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

G 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The Investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IMP. If this delay is outside the screening window specified in schedule of assessments the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in the SoA must be undertaken to confirm eligibility using the same randomization number as for the participant.

G 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service will visit the participants home/or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

G 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication, to be reported and documented.

G 5 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service.

Appendix H National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network guidance for anaphylaxis diagnosis

The National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
  (a) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  (b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
  (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
  (b) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  (c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
  (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that participant (minutes to several hours):
  (a) Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP
  (b) Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person’s baseline

CCI

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I 2 Introduction

CCI

I 3 Objectives

Exploratory	
CCI	CCI
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I 4 Study Design

Only participants who consent to enrol in Part B1 or Part B2 of Study D9450C00001 may participate in CD8+ PET imaging. A separate informed consent is required. Participants must follow all schedules and procedures in the main protocol, unless otherwise specified in this Appendix.

Participants will be administered a CCI mL dose of ^{89}Zr-Df-crefmirlimab tracer by i.v. infusion during screening (D-14 to D-1) and at one timepoint on treatment (D29 for participants receiving AZD8853). Imaging to be done only after the participant's eligibility for the study has been confirmed. The D29 tracer infusion may be delayed after discussion with Study Physician. Positron emission tomography/CT scan must be conducted within 24 (± 3) hours (preferred) but no later than 72 hours after the tracer infusion and prior to the biopsy.

Positron emission tomography/CT scan images must only be acquired on PET/CT scanners that have been approved by ImaginAb or its representative. The same scanner should be used throughout the participant's time on study. Whole body scans should be obtained at every scan visit. Please refer to the current imaging manual regarding participant preparation, scanning times per bed position, ^{89}Zr-Df-crefmirlimab optimization, acquisition and reconstruction

parameters, slice thickness and other parameters as well as instructions for how to submit images for review (Note: Important for the sites to follow the instruction in Imaging Manual).

I 5 Schema

Figure 4 illustrates CD8+ PET and mandatory biopsies timelines in Part B1 and Part B2: AZD8853 Expansion.

I 6 Benefit-Risk Assessment with ^{89}Zr-Df-Crefmirlimab (CD8+ PET Tracer)

The safety monitoring practices employed in the main protocol (Section 8.2, Section 8.3) are adequate to protect the participant safety for this part of the study. Preclinical data, both in vivo and in vitro have demonstrated that ^{89}Zr-Df-crefmirlimab had no measurable effect on T cell proliferation, activation or cytokine release. An imaging investigating the use of ^{89}Zr-Df-crefmirlimab as a non-interventional or a treatment modality is not likely to improve response to treatment. However, should CD8+ PET imaging show a direct correlation to TIL recruitment to the TME, future cancer patients may be spared from painful invasive biopsies. Moreover, a positive correlation to clinical outcome could, in the future, potentially allow more rapid assessment of whether patients are responding to therapy and allow physicians to make decisions earlier about continuing or switching therapies for their participants.

Potential risks include infusion site reactions (eg, redness, itching and pain), allergic reaction (including anaphylaxis), renal failure, hepatic failure, arthritis, and/or hypotension.

For information on all identified and potential risks of crefmirlimab refer to the current version of the ^{89}Zr-Df-crefmirlimab IB.

I 7 Study Population

Parts B1 and B2 of the study have no additional inclusion/exclusion criteria for CD8+ PET imaging compared to the overall study, except known allergies to CD8+ PET tracer. For further details on the study population refer to Section 10.5.

I 8 Investigational Imaging Agent

For participants enrolled in Parts B1 and B2 for CD8+ PET imaging, an investigational imaging agent will be utilized, an anti-CD8 minibody (crefmirlimab), conjugated with Df and radiolabelled with ^{89}Zr (^{89}Zr-Df-crefmirlimab):

- Pharmacological Class: A biological PET radioligand for detecting CD8+ T cells
- Dosage Formulation: CCI [redacted]
- Route of Administration: i.v. infusion, between 5 to 10 minutes.

I 8.1 Investigational Product Storage

The dose will be delivered by a central manufacturing facility to the investigational site's radio pharmacy or Nuclear Medicine Department. Each shipment of ^{89}Zr-Df-crefmirlimab will arrive in a thermally controlled shipping system. Investigational product is stored in a secure refrigerator at 2°C to 8°C, housed inside a sealed lead pot until one hour before the time of infusion. The dose of ^{89}Zr-Df-crefmirlimab should be dispensed and administered by the expiration time listed on the label.

I 8.2 Investigational Product Handling

The ^{89}Zr-Df-crefmirlimab dose will be measured by the qualified personnel in a dose calibrator prior to dispensing. Then the syringe will be placed in a shielded carrier along with a designated i.v. infusion pump for radioactive infusion and administration. After the dose administration, the qualified personnel will return the syringe for residual measurement by the nuclear pharmacist at the site. Measured radioactivity values and times of measurement will be documented, as well as the total injected volume.

I 8.3 Treatment Administration

The dose of ^{89}Zr-Df-crefmirlimab should be removed from the secure refrigerator 1 hour before the time of infusion in order for the dose to come to room temperature. A single dose of the investigational imaging agent, ^{89}Zr-Df-crefmirlimab [CCI [redacted] mL] will be drawn up into a syringe according to the site's schedule of procedures. Site personnel will label the syringe with the completed investigational imaging agent label and log the dose in the radio pharmacy standard drug use logs.

For further information see the ^{89}Zr-Df-crefmirlimab Imaging Manual.

I 9 Statistical Considerations

The sample size for CD8+ PET imaging is not based on statistical power calculations. It was determined by practical considerations and to provide data to enable the relationship between CD8+ PET imaging and the paired biopsy data to be explored, taking into account dropouts. Up to approximately 20 participants enrolled into Part B of the study will participate in CD8+ PET imaging.

To meet objectives of CD8+ PET imaging, the following endpoint will be evaluated:

- Standardized uptake value quantitative measures of tumour lesions (biopsied and non-biopsied) and reference tissues; SUV values will be calculated at and between timepoints.

Positron emission tomography data are converted to lean body mass SUVs, using the participant's height, weight, and injected activity.

Descriptive statistics will be used to describe the SUV measurements of tissues of interest (eg, tumour, lymph node). Categorical data will be summarized by counts and percentages. Continuous variables will be summarized by mean, median, standard deviation, minimum, and maximum.

The relationship between SUV measurements of tissue and CCI or IHC of innate, and adaptive immune cells/factors from tumour biopsies from the main protocol will be explored.

Efficacy endpoints from the main protocol (ORR, DoR, PFS, and OS, where possible) will be assessed in relation to SUV measurements.

Any results from such analyses may be reported separately from the CSR.

Appendix J Abbreviations

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase gene
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
BICR	Blinded Independent Central Review
BMI	Body mass index
BoR	Best overall response
BP	Blood pressure
CAP	College of American Pathologists
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA	Clinical laboratory improvement amendments
Cmax	Maximum concentration
CNS	Central nervous system
CONSORT	Consolidated standards of reporting trials
COVID-19	Coronavirus disease 2019
CPI	Checkpoint inhibitors
CR	Complete response
CRC	Colorectal cancer
CRO	Contract research organisation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumour deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte associated protein 4
DC	Dendritic cells

Abbreviation or special term	Explanation
DCR	Disease control rate
DCO	Data cut-off
Df	Deferoxamine
DILI	Drug induced liver injury
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
ECOG	Eastern cooperative oncology group
EDC	Electronic data collection
EGFR	Estimated glomerular filtration rate
EMA	European medicines agency
EoI	End of infusion
EOT	End of treatment
FDA	Food and drug administration
FDG	^{18}F-Fluoro-deoxyglucose
Fc	Fragment crystallizable
FFPE	Formalin-fixed paraffin-embedded
FTiH	First time in human
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GDF15	Growth differentiation factor 15
GLP	Good laboratory practice
GRFAL	Glial cell line-derived neurotrophic factor (GDNF) family receptor α-like
HAV	Hepatitis A virus
Hb	Haemoglobin
HbA1c	Haemoglobin A1c
HBc	Hepatitis B core
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCP	Health care professional
HCV	Hepatitis C virus

Abbreviation or special term	Explanation
HEV	Hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency viruses
HL	Hy's Law
HNSTD	Highest non-severely toxic dose
HPDD	Highest protocol defined dose
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICD	Immune complex disease
ICF	Informed consent form
ICH	International Council for Harmonisation
iCRO	Imaging Contract Research Organisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
imAE	Immune mediated adverse event
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional Review Board
IRR	Infusion related reactions
IxRS	Interactive voice/web response system
IRT/RTSM	Interactive Response Technology System/Randomisation and Trial Supply Management
i.v.	Intravenous
LTFU	Long term follow-up
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
CCI	[redacted]
MoA	Mechanism of action
MSS	Microsatellite stable
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
CCI	CCI [redacted]
mTPI	Modified toxicity probability interval

Abbreviation or special term	Explanation
NASH	Non-alcoholic steatohepatitis
NCI	National Cancer Institute
NE	Not evaluable
NIMP	Non-investigational medicinal product
NK	Natural killer
NL	New lesion
NSCLC	Non-small-cell lung cancer
NTL	Non-target lesions
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall Survival
OTC	Over-the-counter
CCI	CCI
PD	Pharmacodynamics
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
PEF	Peak expiratory flow
PET	Positron emission tomography
PFS	Progression free survival
PHL	Potential Hy's Law
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
Q3W	Every 3 weeks
Q9W	Every 9 weeks
Q12W	Every 12 weeks
Q26W	Every 26 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cells
RECIST	Response evaluation criteria in solid tumours
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RT-qPCR	Reverse transcription-quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation or special term	Explanation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Stable disease
SMI	Skeletal muscle index
SoA	Schedule of activities
SOC	System organ class
SRC	Safety review committee
SUV	Standardised uptake value
T3	Triiodothyronine
T4	Thyroxine
TBD	To be decided
TBL	Total bilirubin
TGF-β	Transforming growth factor beta
Th1	T helper type 1 cells
TIL	Tumour infiltrating lymphocyte
TL	Target lesion
TME	Tumour immune microenvironment
TMG	Toxicity management guidelines
TPV	Third party vendor
Treg	Regulatory T cells
TSH	Thyroid-stimulating hormone
UC	Urothelial carcinoma
ULN	Upper limit of normal
UPM	Unit probability mass
WBC	White blood cells
WOCBP	Women of childbearing potential
w/v	% weight per volume
Zr	Zirconium

Appendix K Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 29 November 2021

Overall Rationale for the Amendment:

This amendment is considered to be a global substantial amendment based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of European Union.

This protocol amendment incorporates changes requested by the United States Food and Drug Administration (FDA).

A high-level description of the changes is provided in the table below.

Section(s)	Description of Change
Title	Title updated to remove “Modular” language
Entire Protocol	• References to “Core Protocol” changed to “Master Protocol” throughout the entire document • References to “Module 1” or “Module #” changed throughout the entire document to “Substudy 1” or “Substudy #” • Updated urothelial bladder cancer (UBC) to urothelial carcinoma (UC) throughout for consistency • Updates made for clarity and consistency, including the correction of grammar and/or spelling.
Sections 1 to 9	Changed from “Core Protocol” sections to “Master Protocol” sections
Sections 1.1, 4.1.1, 4.1.2	Addition of clarified study design details
Sections 1.2, 10.1.1	Study schema in Figure 3 (Section 10.1.1), which provides details on Substudies, copied to Section 1.1 (Figure 2)
Section 2.3.1	Sentence added to clarify that the TMG is provided as a separate document.
Section 4.4.1	Study Stopping Criteria updated to require halting enrolment in the event of unacceptable toxicity
Section 10	Changed from “Module 1” to “Substudy 1”
Section 10.8	Blood volumes updated.
Sections 10.1.2, Table 13; 10.8.5.1 Table 18	Additional pharmacokinetic (PK) timepoints added for Substudy 1 Parts B and C
Sections 10.1.2 Table 13; 10.8.2.1 Table 17	Table added to clarify electrocardiogram collection timepoints
Section 10.1.2 Table 13	Correction of footnotes for clarity
Sections 10.4.1, 10.6.7	Clarified Recommended Phase 2 dose (RP2D) will be defined in Dose Expansion parts of the Substudy 1

Section(s)	Description of Change
Section 10.5.1	Growth differentiation factor 15 (GDF15) cut off of ≥ CCI pg/mL specified
Section 10.6.8	• Clarified language regarding relatedness of adverse events in the Dose limiting toxicity (DLT) definition • Removed DLT exception for Grade ≥ 3 endocrine disorders • Separated exception to DLT criteria for elevated amylase / lipase and electrolyte abnormalities

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Clinical Study Protocol – Addendum – Global No. 2	
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Study Code	D9450C00001
Addendum Version	2.0
Date	24 June 2022

Global Addendum No. 2

A Phase I/IIa First-in-human, Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of AZD8853 in Participants with Selected Advanced/Metastatic Solid Tumours

Sponsor Name: AstraZeneca

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s):

IND number: 157890

EudraCT number: 2021-005438-41

Protocol Number: D9450C00001

Corresponding Protocol Versions:

Amendment 2.0, v3.0 (11 April 2022)

Amendment 1.0, v2.0 (03 December 2021)

1. DOCUMENT HISTORY

DOCUMENT HISTORY	
Document	**Date**
Global Addendum 2 (v2.0)	24 June 2022
Protocol Amendment 2 (v3.0)	11 April 2022
Global Addendum 1 (v1.0)	30 Mar 2022
Protocol Amendment 1 (v2.0)	03 Dec 2021

Overall Rationale for the Addendum:

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of European Union.

The primary reason for this addendum is to implement a washout period for prior radiotherapy and standard of care treatment. This addendum should be implemented immediately due to possible patient safety implications, regardless of current approved protocol version.

These changes will be incorporated in the next global protocol amendment.

Section # and Name	Description of Change with Reason
5.1 Inclusion Criteria – Prior / Concomitant Therapy	Add 2 new criteria: • *Wide-field radiotherapy must be completed at least 28 days before the first dose of study intervention. However, limited-field, palliative radiotherapy may be administered up to 7 days before the first dose of study intervention.* • *Systemic standard of care (SOC) therapy must be completed at least 28 days, or 5-half-lives of the SOC therapy, whichever is shorter, prior to the first dose of study intervention.* While the protocol has other defined washout periods, there is not a clear washout for radiotherapy and standard of care therapies. Clear washout periods are necessary for patient safety, and for supporting a clear safety profile.

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