STATISTICAL ANALYSIS PLAN	
Study Code	D9450C00001 (AZD8853)
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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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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BOR	Best Overall Response
BSR	Baseline Scaled Ratio
CCr	Creatinine Clearance Rate
CD8	Cluster of differentiation 8
CI	Confidence Interval
CL	Clearance
CL/F	Apparent Clearance
CPQP	Clinical Pharmacology and Quantitative Pharmacology
CPS	Clinical Pharmacology Scientist
CR	Complete Response
CRF	Case Report Forms
CSP/PROTOCOL	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computerised Tomography
CTAE	Cancer Institute Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumour Deoxyribonucleic Acid
CV	Coefficient of Variation
DBL	Data Base Lock
DCO	Data Cut Off
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DMPK	Clinical Pharmacology & Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
DoR	Duration of Response

DU	De-escalate to the previous lower dose and the current dose is never used again due to unacceptable toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
F	Absolute bioavailability
FAS	Full Analysis Set
Frel	Relative bioavailability
gCV	Geometric Coefficient of Variance (%)
GFR	Glomerular Filtration Rate
gmean	Geometric mean
CCI	CCI [redacted]
HPDD	Highest protocol defined dose
ICD	Immune complex disease
ICF	Informed Consent Form
IHC	Immunohistochemistry
IP	Investigational Product
IPD	Important Protocol Deviation
iRECIST	Immune response evaluation criteria in solid tumours
IRR	Infusion related reactions
ITT	Intention to treat
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Max	Maximum
MoA	Mechanism of Action
MRI	Magnetic Resonance Imaging
CCI	[redacted]
MSS-CRC	Microsatellite Stable-Colorectal Cancer
MTD	Maximum Tolerated Dose
mTPI-2	Modified Toxicity Probability Interval-2
NC	Not Calculable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Non-evaluable
NED	No Evidence of Disease
NQ	Non-Quantifiable

NR	Not Reportable
NS	No Sample
NSCLC	Non-Small-Cell Lung Cancer
NTL	Non-Target Lesion
OAE	Other significant Adverse Events
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PAVA	Pool Adjacent Violators Algorithm
PD	Pharmacodynamics
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PDAP	Protocol Deviation Assessment Plan
PDT	Protocol Deviation Tool
PT	Preferred Term
QTcF	Fridericia's correction
Rac	Accumulation Ratio
Rac	Accumulation Ratio
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMI	Skeletal Muscle Index
SOC	System Organ Class
Std Dev	Standard Deviation
SUV	Standardised uptake value
TCP	Temporal Change Parameter
TEAE	Treatment-Emergent Adverse Events
TFL	Tables, Figures, Listings
TL	Target Lesion
TNM	Tumour, Nodes, and Metastases
UC	Urothelial carcinoma
ULN	Upper Limit of Normal range

WHODrug	World Health Organisation Drug Dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	18/08/2022	Initial approved SAP	N/A	N/A
Version 2.0	04/01/2023	• Section 2 – Changes to protocol planned analyses: - The following bullet point has been added to section 2: "At the completion of Substudy 1 Part A, all appropriate data will be presented to answer the primary analysis endpoint which will evaluate Dose Limiting Toxicities (DLTs) and determine the MTD. This deviates from the protocol which suggests all data will be presented. Presenting data only applicable to the primary endpoint of Part A, ensures the question is sufficiently answered in a timely manner, and prevents other data not needed for this endpoint being analyzed too early and too often during the study which could have a detrimental affect trial integrity."	No (Planned change).	Added further clarification to what will be presented in the Primary analysis of Part A.

		• Section 3.1: - The following text has been added to paragraph 1 “Participants who have completed study may have their data frozen once their data is clean”. - Added clarification that data (from previous Substudies) will not be re-analysed at the completion of all Substudies. - Final analysis definition has been amended slightly in section 3.1 to include ‘End of study will be based on the last sub-study open’.	All changes are in line with the CSP.	Add further clarification to the timing of analysis
		• Section 3.1.1: Added in the primary analyses to be conducted at the completion of each Part in Substudy 1 (as per Table 22 Protocol version 3). This also includes additional information on data cut-offs and data lock. Table 1 has also been updated for this information.		To add in the primary analyses after Part A of Substudy 1
		• Section 3.2 - Table 2: - Removed immunogenicity listings from Table (included in Version 1.0 in error).		Immunogenicity included in error; it is already being presented in Safety analysis set.
		- Referenced additional information on DLT analysis set as added in the exposure section 4.2.1.1.		Additional guidance provided on how to derive DLT analysis set

		• Section 3.3.2: Additional information has been added regarding visit windows and missing visit dates: “In the scenario that a complete visit date falls into the same visit as one that has been assigned due to missing data, the visit with the complete date is summarised”		Added to further clarify how this data would be handled.
		• Section 3.3.5: Added that protocol deviations will be reviewed before the end of database lock and prior to the data cut-off for any primary analyses		Protocol deviations need to also be reviewed prior to primary analyses (I.e. Substudy 1, Part A) where a data cut-off is used.

		• Section 3.3.6: Additional information has been added into the 'Missing dates' section. This provides more specific information about the date that should be imputed: • For the imputation of missing AE and concomitant medication end dates, where the date is completely missing, additional information has been added to the following text: "Or if it started on or after first dose date then impute a date that is after the last dose of study drug date'. Added e.g., the day after." • Additional information added to clarify the imputation of data where a participant is known to have died: "If a participant is known to have died where only a partial death date is available, then the date of death is imputed according to the rules for imputing AE start dates unless this date is before the last date the patient is known to be alive from the database" - Added 'In this scenario, the day after the last known alive date should be imputed.' • Section 3.3.6: Additional information has been added into the 'Missing dates' section with reference to subsequent cancer therapy. This allows a more conservative approach to the imputation of subsequent therapy start date, which means more AEs will be treatment emergent: - "Missing day - impute the last day of the month unless both the month and the year are the same as the last dose date or the primary analysis DCO date then impute the		Added to further clarify how this data would be handled.

		last dose date +1 day or the primary analysis DCO date. - Missing day and month - impute 31st December unless the year is the same as the last dose date or the primary analysis DCO date then impute the last dose date + 1 day or the primary analysis DCO date. - Impute last IP dose date + 1 day - Imputed start date should be no earlier than the last IP dose."		
		• Section 4.1.1.2 - Added participants who completed treatment into 'participant demographics' table as discussed in TFL CRM. - Removed covid pandemic text. This will be replaced with "Global/ country situation" as we collect information in the CRF on this rather than COVID-19.		Added to bring summarises in line with the data we collect in the CRF
		Section 4.1.3.2: • Protocol deviations, presentation. Changed IPDs relating to 'Global\ country situation' to IPDs relating to COVID-19, as PDs are reviewed and those relating to COVID-19 are indicated only. • Number and percentage of participants with each IPD is presented for each category; At least 1 IPD, at least 1 Covid-19 related IPD, at least 1 IPD excluding COVID-19 related IPDs.		Added to bring summarises in line with what is collected.

		• Section 4.1.4 – Demographics presentation – Removed ‘suspected’ COVID-19 from the description, as we do not collect suspected COVID-19. Demographic data will only be presented for participants who have confirmed COVID-19 (if data allows).		Added to bring summarises in line with what is collected.
		• Section 4.1.6.1 – Disease characteristics: - Definition and derivations. Correction made to an error in the derivation of ‘Time since last cancer therapy’ and ‘Time since most recent date of progression’ as these should be derived in days rather than years. - removed AJCC at study entry as we only collect this information at diagnosis - Added the number of metastatic sites, to present within the demographics section.		Correction of derivation. Added to bring summarises in line with what is collected. As requested from the Part A TLF CRM.
		• Section 4.2: Text prior to Table 3 has been reworded slightly so the grammar makes more sense.		Correction of grammar.
		• Section 4.2.1.2 – Amended text so AEs >=Grade 3 are presented, rather than Grade 3 and 4. • Section 4.2.1.6 – Vital signs – Reference ranges need to be presented for vital signs. These have been added in Table 6 using the cleaning alert ranges from the medical monitoring report.		As requested from the Part A TLF CRM. Added so reference ranges for vital signs can be presented in the TLFs.
		• Section 4.2.8.2 – Secondary endpoint overall survival, derivations: Added 'Physical examination, ECOG and ECG dates' into the list of dates to use for last known alive date.		Added to bring summarises in line with what is collected.

		• Section 4.2.3.2 - Best Overall Response Derivation: - Updated the derivation for patients who dies with no evaluable RECIST assessments as per guidance given in AZ SAP Template: AZ SAP guidance is the following:" XX weeks is defined as within 2 visits of baseline, plus [e.g. 1] week to allow for a late assessment within the protocol visit window." This was incorrectly included as 10 weeks in version 1 but should be 16 weeks (6 weeks + 9 weeks + 1 week) as per guidance. - Updated the derivation for stable disease. The current definition incorrectly allows for an early assessment within the assessment window, which is not specified in the protocol for assessments done at week 6, meaning a cut-off of 5 weeks is incorrectly being used rather than 6 weeks. As per the protocol, SD should only be reported if more than 6 weeks after first dose. • Section 4.2.4.1 – Disease control rate at week 15 - Definition: Definition of disease control as a BOR of SD (without subsequent cancer therapy) has changed from being maintained from 14 weeks to 15 weeks from first IP, as a 1-week early assessment is not allowed in the protocol. Removed "confirmed PR or CR or >16 weeks from first IP". Followed AZ early oncology template: "Disease control is defined as a BOR of confirmed CR or PR or		Correction of derivation and definition.

		having SD (without subsequent cancer therapy) maintained for ≥ 15 weeks from first IP." • Section 4.2.6.2 – Progression Free Survival Derivation: Updated the derivation for calculating two missed visits when considering RECIST assessment at Week 6 and Week 15. As per the protocol, these two visits do not allow for early assessments, which was incorrectly considered in SAP Version 1.0. • Section 4.2.7.2: Change in Target Lesion Derivation: As per the protocol, we do not allow for an early assessment of RECIST at Week 6 or Week 15 assessments, therefore the +/- has been removed, allowing for late assessments only: "RECIST v1.1 scan performed within W6(D1-D7), W15(D1-D7)."		
		• 'RECIST' updated to 'RECIST v1.1' throughout. • Sub-study and Substudies changed to Substudy and Substudies respectively throughout.		Clarify the version of RECIST we use throughout. Ensure consistency throughout the SAP.

Version 3.0	28/06/2023	The RECIST timepoints are incorrectly defined in the SAP, the study weeks does not equal the time following first IP, for example, the first RECIST assessment is expected at study week 6, which is 5 weeks following first IP rather than 6 weeks following first IP which was incorrectly being used in the SAP. • Section 4.2.3.2 - Best Overall Response Derivation: o Updated the derivation for patients who dies with no evaluable RECIST assessments. The current definition incorrectly defines the first assessment timepoint at 6 weeks after 1st IP dose instead of 5 weeks o Updated the derivation for stable disease. The current definition incorrectly defines the first assessment timepoint at 6 weeks after 1st IP dose instead of 5 weeks. • Section 4.2.4 – Disease control at Study week 15: o Disease control rate updated to be at study week 15 (14 weeks after first IP)., rather than at 15 weeks. • Section 4.2.6.2 – Progression Free Survival Derivation: o Updated the definition of two missing consecutive visits, based on the correct RECIST timepoints. • Section 4.2.7.2 – Change in Target Lesion Tumour Size Derivation: • Clarified it is Study week 15, rather than week 15 throughout.	All changes are in line with the CSP.	Correction of RECIST time windowing as per protocol.

		• Section 4.1.4 – Demographics: o Further detail added about Nicotine summarises and the derivation of number of pack years. • Section 4.1.6 – Disease Characteristics o Time since most recent date of progression derived in days, but label says "months". Text has been updated so it also says days • Section 4.2.1.7 – ECG: o Added normal reference ranges into the SAP for ECG variables. • Section 4.2.1.3 - Clinical Laboratory, Blood Sample o Included definition for clinically significant on-treatment values worse than baseline. • Section 4.2.1.4 - Clinical Laboratory, Urinalysis: o Included definition for clinically significant on-treatment values worse than baseline. • Section 4.2.1.1 -Exposure: o Total duration of safety follow-up derivation and summary has been removed.		Added to further clarify how this data will be derived and handled. Updated to be consistent with the definition. ECG variables required for derivations in the TLF Outputs. Added clarification on definition. Does not follow AZ TLF standards.

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D9450C00001 supporting the Clinical Study Report (CSR). This is a first-in-human Phase 1/2a, multicenter, open-label, dose escalation and dose expansion study to evaluate the safety, tolerability, preliminary anti-tumour activity, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of AZD8853 in patients with selected advanced/metastatic solid tumour. The reader is referred to version 3.0 (dated 11 Apr 2022) of the Clinical Study Protocol (CSP) and the electronic Case Report Form (eCRF) for details of objectives, study design, study conduct and data collection. The Statistical Analysis Plan (SAP) should be read in conjunction with the CSP.

The study currently includes 1 "Substudy", which has 3 parts: Part A (dose escalation), Part B (Pharmacodynamics [PD]/ Mechanism Of Action [MoA] Expansion) and Part C (Efficacy Expansion). Part B includes Part B1, in which up to approximately 20 participants (approximately 10 Microsatellite Stable-Colorectal Cancer (MSS-CRC) participants and approximately 10 Non-Small-Cell Lung Cancer (NSCLC) participants) receive an alternative dose of Investigational Product (IP), and part B2 in which, up to approximately 20 participants (approximately 10 MSS-CRC and approximately 10 NSCLC participant) receive an IP at Maximum Tolerated Dose (MTD)/Highest Protocol Defined Dose (HPDD). In addition, up to approximately 20 participants who consent in part B1 or Part B2 of the study may also participate in cluster of differentiation (CD)8+ positron emission tomography (PET) imaging, which has additional endpoints. Part C includes Part C1, in which up to 40 participants (first indication) received IP at MTD/HPDD, and Part C2, in which up to 40 participants (first indication) received IP at an alternative dose, or up to 40 participants (second indication) received IP at MTD/HPDD.

Further combination Substudies may be added into the CSP once a Recommended Phase 2 Dose (RP2D) for monotherapy has been identified. The SAP will be updated accordingly if further Substudies are added. Each section of the SAP describes the general analysis applicable to all Substudies and parts. Substudy specific analysis will be described under the relevant subheading.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The following changes have been applied to this version of the SAP and are pending update in the protocol:

- The end of study definition in CSP section 4.4 will change from last IP dose to first IP dose, "The end of study is defined as 18 months after the last enrolled participant received his/her first dose of study IP or when the sponsor stops the study, whichever occurs first."

- The definition of screen failures, in CSP section 5.4, will change in the protocol. Screen failures are patients who have been enrolled but failed to meet the study inclusion/exclusion criteria.
- At the completion of Substudy 1 Part A, all appropriate data will be presented to answer the primary analysis endpoint which will evaluate Dose Limiting Toxicities (DLTs) and determine the MTD. This deviates from the protocol which suggests all data will be presented. Presenting data only applicable to the primary endpoint of Part A, ensures the question is sufficiently answered in a timely manner, and prevents other data not needed for this endpoint being analyzed too early and too often during the study which could have a detrimental affect trial integrity.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Participant data will be locked prior to the final analysis of each Substudy, and outputs will be produced and reported in a CSR. Participants who have completed study may have their data frozen once their data is clean. Further details are provided under each study subsection.

Data will be hard locked once all Substudies are completed, and data will be presented per Substudy (and part if applicable) within a CSR, using the Data cut-off (DCO) of the primary analysis within each Substudy. Analyses already completed within previous Substudies will not be re-run at the hard lock. Additional information on how the data will be presented for each Substudy is provided in the corresponding sections of the SAP.

The final analysis of the study is planned 18 months after the last enrolled participant received his/her first dose of study IP or when the Sponsor stops the study, whichever occurs first. End of study will be based on the last Substudy open.

Further details on the analyses planned are provided in Table 1.

3.1.1 Substudy 1

For Substudy 1, data is presented separately for part A, B and C. For part A data is presented by dose level and overall. For part B, data is presented in separate tables by tumour type, by dose level and overall. For part C, data is presented in separate tables for indication by dose level (as applicable at the time). No direct statistical comparisons will be made between any cohorts or expansions.

One interim analysis is planned for Part C in this Substudy. Recruitment will not be paused while the participants required for the interim analysis are being evaluated.

At the completion of each part within Substudy 1, a primary analysis will be conducted (analysis will be conducted separately for each part).

Table 1: Timing of analysis

Analysis	Trigger	Data Type Included
Final analysis	The end of the study is defined as 18 months after the last enrolled participant received his/her first dose of study IP or when the Sponsor stops the study, whichever occurs first.	All data*
Substudy 1		
Interim for efficacy expansions (Parts C1 and C2)	After the 20th participant in each expansion had the opportunity for 2 on-treatment RECIST assessments	Efficacy (RECIST v1.1 ORR, DoR, DCR at 15 weeks, PFS, OS and tumour size) Safety
Primary analysis	At completion of each part (primary analysis is conducted separately for each part):	All appropriate data

DCR = disease control rate; DoR = duration of response; IP = Investigational Product; ORR = objective response rate; OS= Overall Survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1; PFS = Progression Free Survival.
*Data will be presented by part at the final analysis of the Substudy, except for safety analyses, which will be presented by part and for Part A + Part B if same patients and same dose (See section 4.2).

3.2 Analysis Populations

All participants who receive any amount of IP are included in the Safety analysis set. For the safety and PK analyses, participants are classified according to the IP starting dose. For all efficacy analyses, and for baseline and demography, participants are classified according to the dose they were assigned to (i.e., the planned IP dose level).

The following populations are defined in Table 2.

Table 2: Populations for Analysis

Population/Analysis set	Description	Endpoint/Output
Enrolled	All participants who sign the ICF	Disposition
Safety	All participants who receive any amount of IP.	Baseline and demographics Exposure Safety endpoints PK concentrations listings

Population/Analysis set	Description	Endpoint/Output
		PK parameters listings Immunogenicity listings PFS OS ctDNA
DLT Evaluable	Enrolled participants who complete the DLT evaluation period (defined as 21 days after receiving the first infusion of IP) with at least 75% dosing* and have completed safety evaluation requirements during the DLT evaluation period, as defined in the CSP OR Patients who experience any DLT during the DLT evaluation period.	DLT
Response Evaluable	All dosed participants who have measurable disease at baseline.	ORR DoR BoR DCR at 15 weeks Percentage change in tumour size
Pharmacokinetics	All participants who receive at least one dose of IP with at least one reportable concentration. **	PK concentrations PK parameters
Immunogenicity	All participants who receive at least one dose of IP who have a non-missing baseline ADA result and at least 1 non-missing post-baseline ADA result	Incidence of ADA ADA titer
Substudy 1 Population		
Interim Response Evaluable (Interim – Expansion only)	All dosed participants who had measurable disease at baseline and have had the opportunity for 2 on-treatment RECIST assessments (16 weeks, 6+9 weeks + 1 week window) or have had 2 on schedule tumour assessments.	ORR at interim DoR BoR at interim Tumour size
Pharmacodynamics	All participants who receive at least one dose of IP with baseline measurement and at least one	Change in circulating GDF15 serum levels (applicable for Part A and Part B only).

Population/Analysis set	Description	Endpoint/Output
	reportable pharmacodynamic measurement.	Change in CD8 tumour infiltration by IHC using baseline and on treatment samples (applicable to Part B only).

ADA=Anti-Drug Antibody; BoR=Best Overall Response; CD8=cluster of differentiation 8; ctDNA=circulating tumour deoxyribonucleic acid; DCR=disease control rate; DLT=dose limiting toxicity; DoR=duration of response; FAS = Full analysis set; ICF= informed consent form; IP= Investigational product; ITT=Intention to treat; PET=positron emission tomography; PFS=Progression Free Survival; PK=pharmacokinetics; PD=pharmacodynamics; OS= overall survival; ORR= objective response rate; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.
*Please refer to section 4.2.1.1 for the derivation of percentage of dosing.
** Individual PK concentration and parameter data for any participants who are excluded from the descriptive summary tables, figures and/or inferential statistical analyses are included in the listings and are flagged with an appropriate footnote.

3.3 General Considerations

Data for Substudy 1 is presented separately for part A, B and C. For part A data is presented by dose level and overall. For part B, data is presented in separate tables for tumour type, and by dose level and overall (in each column of the tables). For part C, data is presented in separate tables for indication or by dose level (as applicable at the time).

3.3.1 General Study Level Definitions

The general principles described below are followed throughout the study:

- Continuous endpoints are summarised by the number of observations, mean, standard deviation (Std Dev), median, upper, and lower quartiles (as applicable), minimum, and maximum. For data that requires log-transformation, it is more appropriate to present geometric mean, Coefficient of Variation (CV), median, minimum, and maximum. Categorical endpoints are summarised by frequency counts and percentages for each category.
- If data are available for less than three participants, no summary statistics other than minimum, maximum, and number of observations are presented.
- Unless otherwise stated, percentages are calculated out of the analysis set total (excluding efficacy and exposure) and for dose cohort by time point and tumour type as appropriate.
- For continuous data, descriptive summary statistics (mean, median, Std Dev, standard error, Confidence Intervals [CIs]) are rounded to one additional decimal place compared to the original data. Minimum and maximum are displayed with the same accuracy as the original data.
- For categorical data, percentages are rounded to 1 decimal place.
- SAS® version 9.4 (as a minimum) is used for all analyses.

- Baseline is the last non-missing value obtained prior to the first dose/administration of any IP and any information taken after first dose/administration of IP is regarded as post-baseline information. If two visits are equally eligible to assess participant status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration with no washout or other intervention in the screening period), the average is taken as the baseline value. For non-numeric laboratory tests (i.e., some of the urinalysis parameters) where taking an average is not possible then the best value is taken as baseline as this is the most conservative. In the scenario where there are two assessments on Day 1 prior to first dose, one with time recorded and the other without time recorded, the one with time recorded is selected as baseline. Where safety data are summarised over time, study day is calculated in relation to date of first treatment. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, serves as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured is considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose. If no value exists before the first dose/administration, then the baseline value is treated as missing.
- In all summaries, change from baseline endpoints are calculated as the post treatment value minus the value at baseline. The percentage change from baseline is calculated as (post-baseline value - baseline value) / baseline value × 100. For any endpoint subjected to log transformation, the change from baseline calculated and summarised on the log scale are back-transformed and presented as a 'baseline scaled ratio' (BSR). Percentage change is then calculated as (BSR - 1) × 100.
- Unless stated otherwise, two-sided CIs are produced at 90%.
- For the purposes of summarizing safety data assessed at visits, in addition to baseline data, only on treatment data is included in the summary tables. On treatment data is defined as data after the first dose of investigational product (IP) and with assessment date up to and including the date of last IP + 97 days (to consider the ±7 days visit window for the post-treatment follow-up visit planned 90 days after the last dose), and prior to the start of any subsequent cancer therapy.

3.3.2 Visit Window

For safety, time windows are defined for any presentations that summarize values by visit. The following conventions apply:

- The time windows are exhaustive so that data recorded at any timepoint has the potential to be summarised. Inclusion within the time window is based on the actual date and not the intended date of the visit.
- All unscheduled visit data have the potential to be included in the summaries.

- The window for the visits' following baseline is constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit is Day 2). If an even number of days exists between two consecutive visits, then the upper limit is taken as the midpoint value minus 1 day.

  Substudy 1:
  The first 11 visit windows for data between scheduled assessments in this study are:
  - Day 2, visit window 2-4
  - Day 8, visit window 5-11
  - Day 15, visit window 12-18
  - Day 22, visit window 19-25
  - Day 29, visit window 26-32
  - Day 36, visit window 33-39
  - Day 43, visit window 40-52
  - Day 64, visit window 53-73
  - Day 85, visit window 74-94
  - Day 106, visit window 95-115
  - Day 127, visit window 115-136
- Visit windowing are done separately for each assessment based on the schedule of events specific to that assessment
- Should visit date be missing (due to partial or missing dates), then visits are assigned to the nominal visit at which that assessment was recorded, and no windowing is performed.
- For visit-based summaries, if there is more than one value per participant within a time window then the closest value to the scheduled visit date is summarised, or the earlier, in the event the values are equidistant from the nominal visit date. In the scenario that a complete visit date falls into the same visit as one that has been assigned due to missing data, the visit with the complete date is summarised. The listings highlight the value for the participant that contributed to the summary table, wherever feasible. Note: in summaries of extreme values, all post baseline values collected are used including those collected at unscheduled visits regardless of whether the value is closest to the scheduled visit date.
- For summaries at a participant level, all values are included, regardless of whether they appear in a corresponding visit-based summary, when deriving a participant level statistic such as a maximum.

3.3.3 Handling of Unscheduled Visits

See Section 3.3.2.

3.3.4 Multiplicity/Multiple Comparisons

Not Applicable.

3.3.5 Handling of Protocol Deviations in Study Analysis

The definitions of study specific Important Protocol Deviations (IPDs) are provided in the Protocol Deviation Assessment Plan (PDAP). IPDs identified as liable to influence statistical analysis may include, but are not limited to the following types of deviations:

- Participants who deviate from the core entry criteria as per CSP (e.g., Inclusion, exclusion, and discontinuation criteria), and participants who deviate from Substudy specific entry criteria as per CSP.
- Participants who received prohibited medications or therapies.
- Participants where the administration or dosing of IP is not per CSP.
- Procedure/ tests that are outside of required timeframes or not performed as specified in the CSP and are required for trial endpoints.

IPDs are tracked throughout the conduct of the study and reviewed by the study team with the frequency specified in the PDAP. Protocol deviations are evaluated on a case-by-case basis.

None of the deviations lead to the participant being excluded from any analysis sets described in the SAP, unless otherwise specified in the PDAP. If a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed. The need for such a sensitivity analysis is decided during the data review meeting and before the Data-Base Lock (DBL). A list of all protocol deviations is reviewed and all decisions regarding how to handle these deviations are documented by the study team physician, clinical pharmacology scientist (CPS) and statistician prior to DBL and prior to the data cut-off for any primary analyses, in the Protocol Deviation Tool (PDT).

3.3.6 Missing Dates

When partial dates exist in the data there are some general conventions for when the month or day are missing. These are described in the PhUSE guidance on partial dates, which are outlined here.

If the whole date is missing, it is more difficult to follow a general principle, and these are reviewed within the study and decided on how to be handled. General guidance for completely missing dates is provided below, but the guidance is assessed as necessary within the study.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events (AEs) or concomitant medications. The imputed dates should not be used to calculate durations, where the results would be less accurate.

The following are the guidelines used when partial dates are detected in the study:

- For missing diagnostic dates (e.g., disease diagnosis) if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.
- For missing AE and concomitant medication start dates (with the exception of subsequent cancer therapy), the following is applied:
    a. Missing day - impute the 1st of the month unless month is the same as month of the first dose of IP then impute first IP dose date.
    b. Missing day and month - impute 1st January unless year is the same as first IP dose date then impute first IP dose date.
    c. Completely missing - impute first IP dose date unless the end date suggests it could have started prior to this in which case impute the 1st of January of the same year as the end date.
    d. Imputed start date should be no later than the end date.
- For missing AE and concomitant medication end dates, the following is applied:
    a. Missing day - impute the last day of the month unless both the month and the year are the same as the last dose date or the primary analysis DCO date then impute the last dose date or the primary analysis DCO date.
    b. Missing day and month - impute 31st December unless the year is the same as the last dose date or the primary analysis DCO date then impute the last dose date or the primary analysis DCO date.
    c. Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date and when it started in relation to IP. If the ongoing flag is missing, then assume that AE is still present / medication is still being taken (i.e., do not impute a date). If the AE/medication has stopped and start date is prior to first dose date, then impute first dose date. Or if it started on or after first dose date then impute a date that is after the last dose of study drug date (e.g the day after).
- For missing subsequent therapy start dates, the following is applied:

a. Missing day - impute the last day of the month unless both the month and the year are the same as the last dose date or the primary analysis DCO date then impute the last dose date +1 day or the primary analysis DCO date.

b. Missing day and month - impute 31st December unless the year is the same as the last dose date or the primary analysis DCO date then impute the last dose date + 1 day or the primary analysis DCO date.

c. Completely Missing – Impute last IP dose date + 1 day

d. Imputed start date should be no earlier than the last IP dose.

- Flags are retained in the database indicating where any programmatic imputation has been applied, and in such cases for AEs and concomitant medications, any durations would not be calculated.
- If a participant is known to have died where only a partial death date is available, then the date of death is imputed according to the rules for imputing AE start dates unless this date is before the last date the patient is known to be alive from the database. In this scenario, the day after the last known alive date should be imputed. (See section 4.2.8.3 for further details).

3.3.7 Sample Size

Substudy 1

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).

3.3.7.1 Dose escalation: mTPI-2

Part A: Substudy 1

The Modified Toxicity Probability Interval-2 (mTPI-2) employs a simple beta-binomial Bayesian model (Guo et al 2017). The posterior density of the toxicity probability is divided into multiple intervals with equal length. These intervals are categorized as underdosing (below), proper dosing (equivalent), and overdosing (above) in terms of target toxicity. The underdosing interval corresponds to a dose escalation, overdosing corresponds to a dose de-escalation, and proper dosing corresponds to staying at the current dose. The design for the dose-escalation phase of the study uses a target Dose Limiting Toxicity (DLT) rate of CCI% and an equivalence interval CCI for dose-escalation/de-escalation decisions as well as MTD determination. A dose level is 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% (i.e., P [DLT > CCI% | data] ≥ 95%).

For specific dose escalation rules, refer to CSP Section 10.6.6.1.3.

For dose escalation (Part A) cohorts of at least 3 and up to 9 evaluable participants are required for each dose cohort (unless unacceptable toxicity is seen before 3 evaluable participants). 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. More patients may also need to be enrolled to a dose level if toxicity is observed. 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.

The dosing cohorts are grouped depending on the starting dose they are planned. The starting dose for this study is 300 mg with the maximum dose set at 3000 mg.

3.3.7.2 Dose Expansion

Part B: Substudy 1

In the PD/MoA expansions (Part B1 and B2) up to approximately 10 participants may be enrolled in each of 2 dose levels and 2 indications (Non-Small-Cell Lung Cancer [NSCLC] and Microsatellite Stable-Colorectal Cancer [MSS-CRC]) for a total of approximately 40 participants. It is thought that approximately 20 participants enrolled in part B of the study will participate in CD8+ PET imaging.

Part C: Sub Study 1

At least 40 participants will be enrolled in each efficacy expansion (part C1 and C2) 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. The sample size has been determined to provide sufficient precision for the estimation of ORR. With 40 participants in each expansion, CCI [redacted] CI. CIs are constructed around the response rates observed in each population using the Clopper-Pearson method (Clopper and Pearson 1934) to enable decisions to be made about the likely success of future studies in each of the populations. For example:

CCI [redacted]

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation, and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participants screened is defined as informed consent received. Further details are provided in CSP Section 10.5. Participants are followed until either death, lost to follow up or withdrawal of consent or end of study. Participants who permanently discontinue from study intervention remain in the study follow up until death or withdrawal of consent. Further information is defined in CSP section 7.1.

Completion of study is defined in CSP Section 4.4 as 18 months after the last enrolled participant received his/her first dose of IP or when the sponsor stops the study, whichever occurs first.

4.1.1.2 Presentation

Participant disposition including screen failures and reason for screen failure are summarised and listed based on all participants screened (i.e., informed consent received) by the current relevant tables, figures, listings (TFL) standards.

The number and percentage of participants for the following are summarised if applicable:

- Participants screened.
- Screen failures.
- Participants assigned to treatment.
- Participants assigned to treatment, but who were not treated.
- Participants who started treatment.
- Participants ongoing treatment at DCO.
- Participants who discontinued treatment, and reason if applicable.

- Participants ongoing study at DCO.
- Participants who withdrew from study and reason if applicable.
- Participants who completed study

Summaries on disposition due to global/country situation are added to the disposition table if applicable. The number and percentage of participants for the following summaries are added if applicable:

- Participants who discontinued treatment due to global/country situation.
- Participants who withdrew from study due to global/country situation.

Data for each Substudy will be presented as per Section 3.3.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

For the definitions of each analysis set, refer to section 3.2.

4.1.2.2 Presentation

Data for each Substudy will be presented as per Section 3.3.

Any exclusions from analysis sets are listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

The examples of the categories are shown in Section 3.3.5.

4.1.3.2 Presentation

The incidence of IPDs is summarised by deviation categories on the safety analysis set by deviation category. The number and percentage of participants in the following categories are summarised:

- Number of participants with at least 1 IPD.
- Number of participants with at least 1 COVID-19 related IPD.
- Number of participants with at least 1 IPD, excluding COVID-19 related IPDs.

For each summary above, the number and percentage of participants with each IPD is also presented.

A listing is provided with the important protocol deviation details. IPDs resulting from coronavirus disease 2019 (COVID-19) circumstances are also included, if any.

Data for each Substudy will be presented as per Section 3.3.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Age (years) is grouped accordingly in the following categories: < 65, ≥ 65 years. Each race category counts participants who selected only that category.

Number of nicotine pack years is derived as the following:

If nicotine substance use is collected daily:

Number of Nicotine pack years=

Number of nicotine packs per day * Number of years the patient has smoked

If nicotine substance use is collected weekly:

Number of Nicotine pack years=

(Number of nicotine packs per week /7) * Number of years the patient has smoked

4.1.4.2 Presentation

Demographics for Substudy 1 are summarised and listed based on the safety analysis set as defined by the current relevant TFL standards.

The following are summarised:

- Age (years)
- Age group
- Sex
- Race
- Ethnicity

Participant recruitment per country and site is summarised by the safety population.

Participant's substance (nicotine) use, frequency of substance use and number of pack year, is also summarised in a separate table for the safety population.

If data allows (i.e., there are more than 5 participants with this data), demographic characteristics in participants with confirmed COVID-19 infection are summarised, otherwise only listings for these participants are provided.

Data for each Substudy will be presented as per Section 3.3.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Body mass index (BMI) is calculated as:

$$\text{BMI}(\text{kg}/\text{m}^2) = \frac{\text{weight (kg)}}{(\text{height (m)})^2}$$

4.1.5.2 Presentation

Baseline characteristics are listed and summarised for the safety analysis set.

The following are summarised:

- height (cm)
- weight (kg)
- BMI (kg/m²)

Data for each Substudy will be presented as per Section 3.3.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Time from original diagnosis to first dose of IP (in months) is calculated as:

$$\text{Time from original diagnosis (months)} = \frac{(\text{Date of first dose of IP-Date of original diagnosis}+1)}{(\frac{365.25}{12})}$$

Time since last cancer therapy to first dose of IP (in days) is calculated as:

$$\text{Time since last therapy (days)} = (\text{Date of first dose of IP-Stop date of last cancer therapy}+1)$$

Time since diagnosis of metastatic disease to first dose of IP (in months) is calculated as:

$$\text{Time since diagnosis of metastatic disease (months)} = \frac{(\text{Date of first dose of IP-date of first diagnosis of metastatic disease }+1)}{(\frac{365.25}{12})}$$

Time since most recent date of progression to date of first dose of IP (in days) is calculated as:

$$\text{Time since most recent date of progression (days)} = (\text{Date of first dose of IP} - \text{date of most recent progression} + 1)$$

4.1.6.2 Presentation

Disease characteristics at baseline are summarised and listed based on the safety analysis set as defined by the current relevant TFL standards.

Summaries are to be produced that present the number and percentage of participants on their:

- Histology type at diagnosis
- Tumour grade at diagnosis
- American Joint Committee on Cancer (AJCC) stage at diagnosis
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- Primary tumour location at diagnosis
- Local/metastatic sites at study entry
- Tumour Node and Metastases (TNM) classification for primary tumour at time of diagnosis and study entry
- CCI [redacted]
- Location of target lesions at baseline

Summary statistics are presented for participants' time from original diagnosis to first dose (months), time since last cancer therapy (days), time since diagnosis of metastatic disease (months), time since most recent progression (days), number of target Lesions (NTLs), sum of diameter of Target Lesions (TLs) and number of metastatic sites.

Data for each Substudy will be presented as per Section 3.3.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history and relevant surgical history, including both resolved and ongoing conditions at the time of study entry, are summarized by the primary system organ class (SOC) and

preferred term (PT) in accordance with the latest medical dictionary for regulatory activities (MedDRA) at the time of DBL/analysis.

Previous Immunotherapy

The time from most recent immunotherapy to first dose of IP is calculated as:

$$\text{Time since most recent immunotherapy treatment (Days)} = (\text{Date of first dose of IP-end date of last immunotherapy treatment} + 1)$$

The duration of the last immunotherapy prior to study entry is calculated as:

$$\text{Length of last immunotherapy treatment (days)} = (\text{End date of last immunotherapy treatment - Start date of first immunotherapy treatment} + 1)$$

Where last immunotherapy is defined as the last immunotherapy administrated prior to study drug.

The length of all prior immunotherapy prior to study entry is calculated as:

$$\text{Length of all immunotherapy treatments(days)} = \sum_{i=1}^{N} (End\ Date\ of\ immunotherapy\ treatment_i - Start\ date\ of\ immunotherapy\ treatment_i + 1)$$

Where N total number of immunotherapies received by the patient before first dose of IP

4.1.7.2 Presentation

Data for each Substudy will be presented as per Section 3.3.

Medical history, concomitant disease and surgical history are summarised for the safety analysis set by System Organ Class (SOC) and Preferred Term (PT).

Summaries on participants' medical history by system organ class and preferred term are produced.

Previous Cancer Therapy

Summaries of the number and percentage of participants who have had previous cancer treatments are provided by therapeutic class and Anatomical Therapeutic Chemical (ATC) classification and generic drug name for the safety analysis set. The number of regimens of previous anti-cancer therapies at baseline and best response in most recent regimen are summarised as a continuous and categorical variables. Previous treatments are summarised by number of regimens. Previous disease related chemotherapy treatments are summarised by number of regimens, type of treatment and modality. Additionally, the following

characteristics are summarised for previous treatments: generic name, time since last dose, treatment status, treatment duration, best response, reason for therapy failure and platinum sensitivity status at study entry.

Previous Radiotherapy
Summaries of the number and percentage of participants who had at least 1 prior radiotherapy are presented for the safety analysis set. Details on previous radiotherapy are listed.

Previous immunotherapy:

Summary statistics are presented for time from the last immunotherapy treatment to first IP dose (days) and duration of last prior immunotherapy treatment (days). This information will also be presented for immediate immunotherapy, including only patients for whom the last therapy they had prior to study IP was immunotherapy. Summary statistics are presented for the length all immunotherapy treatments.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

For the purpose of inclusion in prior and/or concomitant mediation or therapy summaries, incomplete medication or radiotherapy start and stop dates are imputed as detailed in Section 3.3.6.

Prior medications, concomitant medications and post medications are defined based on imputed start and stop dates as follows:

- Prior medications are those taken prior to IP with a stop date prior to the first dose of IP.
- Concomitant medications are those with a stop date on or after the first dose date of IP and must have started prior to or during treatment so there is at least one day in common with the IP.
- Post-treatment medication are those with a start date after the last dose of IP

4.1.8.2 Presentation

The number and percentage of participants who took prior, concomitant medications, or post treatment medications are summarised and listed for the safety analysis set by ATC code and the generic name/term coded by the World Health Organization Drug Dictionary (WHODrug). Concomitant medications include all concomitant medications taken on or after the date of first dose of study treatment or any concomitant medication started prior to the first dose of study treatment that continued beyond the date of first dose of study treatment.

The number and percentage of participants who have had post-treatment medications, therapy class and agents received are summarised, this includes the number of participants

who have had subsequent anti-cancer therapies, and the best response from subsequent therapy.

Metformin

The number and percentage of participants who took Metformin medication prior to IP treatment are summarised separately if data allows (i.e., more than 5 participants took Metformin treatment), else data are only listed. The time between last dose of Metformin and first dose of IP treatment are also summarised, and can be calculated by the below formula:

$$\text{Time since last Metformin dose (days)} = (\text{Date of first dose of IP} - \text{Date of last Metformin dose} + 1)$$

Data for each Substudy will be presented as per Section 3.3.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, and other endpoints including sensitivity and supportive analyses. Core endpoint analyses are described in Table 3.

Endpoints that are specific to 'Substudy 1' are provided in Table 4. Exploratory analyses for Substudy 1 will be reported separately from the CSR and therefore will be described outside of the SAP.

Table 3: Core Endpoint analysis

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Objective 1: To assess safety and tolerability, characterize DLTs (in dose escalation parts only) and determine the MTD or RP2D of AZD8853 in participants with selected advanced/metastatic solid tumours				
Primary	AEs, SAEs, clinically significant changes from baseline in clinical laboratory parameters, vital signs, and ECG results, Incidence of AEs leading to discontinuation of AZD8853.	Safety analysis set	Percentage of participants with AEs, SAEs, clinically significant changes from baseline in clinical laboratory parameters, vital signs, and ECG results. Percentages of participants with AE leading to discontinuation	4.2.1
Objective 2: To determine the preliminary anti-tumour activity of AZD8853 in participants with selected advanced/metastatic solid tumours				

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Secondary	ORR according to RECIST v 1.1	Response evaluable set	Rate and 90% CI (2-sided CI)	4.2.2
Secondary	DCR at Week 15 according to RECIST v 1.1	Response evaluable set	Rate and 90% CI (2-sided CI) for each cohort at 15 weeks.	4.2.4
Secondary	DoR according to RECIST v 1.1	Subset of response evaluable set: participants with confirmed objective response	Kaplan-Meier plots and median DoR time estimated using Kaplan Meier method.	4.2.5
Secondary	PFS	Safety analysis set	Kaplan-Meier plots and median PFS time estimated using Kaplan Meier method.	4.2.6
Secondary	Change in target lesion tumour size	Response evaluable set	Percentage change in tumour size from baseline, at each timepoint is summarized by mean change and St Dev Percentage change from baseline for each participant is produced over time in a spider plot. Waterfall plots of percentage change from baseline and best percentage change from baseline is produced.	4.2.7
Secondary	OS	Safety analysis set	Kaplan-Meier plots and median OS time estimated using Kaplan Meier method.	4.2.8
Objective 3: To assess the efficacy of AZD8853 using longitudinal blood samples in participants with selected advanced/metastatic solid tumours				
Secondary	Change in ctDNA from baseline	Safety analysis set	Percentage change in ctDNA from baseline to each post baseline timepoint is summarized by mean change and St Dev. Maximum change is	4.2.9

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
			also summarised by mean and St. Dev.	
Objective 4: To determine the PK of AZD8853 in serum when administered in participants with selected advanced/metastatic solid tumours				
Secondary	PK parameters (include but not limited to Cmax and AUC)	PK analysis set	Summary of PK profile of AZD8853	4.2.12
Objective 5: To assess the immunogenicity of AZD8853 in participants with selected advanced/metastatic solid tumours				
Secondary	ADAs against AZD8853 in Serum	Immunogenicity analysis set	Incidence of detectable ADAs against AZD8853 in serum	4.2.13

ADA = antidrug antibodies; AUC = Area Under the Curve; AEs = Adverse Events; CI= Confidence Interval; ctDNA = circulating tumour deoxyribonucleic acid; DCR= disease control rate; DLT= dose limiting toxicity; DoR=duration of response; ECG= Electrocardiogram; MTD = Maximum Tolerated Dose; OS= overall survival; ORR=objective response rate; PFS=Progression Free Survival; PK =pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumours v1.1; RP2D = Recommended Phase 2 Dose; SAEs = Serious Adverse Events; St. Dev = Standard Deviation.

Table 4: Substudy 1 Endpoints

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Objective 1: To assess safety and tolerability, characterize DLTs (in dose escalation parts only) and determine the MTD or RP2D of AZD8853 in participants with selected advanced/metastatic solid tumours.				
Primary (Part A only)	DLTs	DLT evaluable set	Number of participants with DLTs.	4.2.1.8
Objective 6: 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)				
Secondary	Change in circulating GDF15 serum levels	PD analysis set	Actual and percentage change in circulating GDF15 serum levels from pre-treatment (baseline) to each post baseline timepoints as well as the maximum change will be summarised using descriptive statistics such as mean change and St.Dev.	4.2.10

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Objective 7: To evaluate the intra-tumoral PD activity of AZD8853 in participants with selected advanced/metastatic solid tumours (Part B only)				
Secondary	Change in CD8 tumour infiltration by IHC using baseline and on-treatment samples	Subset of PD analysis set (who have paired biopsies)	Change in CD8 tumour infiltration by IHC between the pre-treatment and on-treatment biopsy will be summarised using descriptive statistics such as mean change and St.Dev.	4.2.11

BMI=Body Mass Index; CD8=cluster of differentiation 8; DoR=duration of response; DNA= Deoxyribonucleic acid; IHC=Immunohistochemistry; CCI ; OS= overall survival; ORR= objective response rate; PD=pharmacodynamics; PFS= Progression Free Survival; PK=pharmacokinetics; PET= positron emission tomography; RNA = Ribonucleic acid; SAP = Statistical Analysis Plan; St. Dev = Standard Deviation; SMI= Skeletal muscle index; SUV = Standardized Update Value.

Efficacy analyses, except for OS and ctDNA, are based on programmatic application of Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Eisenhauer et al, 2009) to investigator assessed tumour measurements. Programmatic derivation guidance used for the application of RECIST v1.1 are provided in Appendix A in the Appendices, which is used to determine disease response. RECIST v1.1 data with overall visit response and best objective response are listed.

RECIST v1.1 data, overall visit response and best objective response are listed. Additional listing(s) are produced for tumour assessments per patient, BOR, DOR, DCR.

Substudy 1

For Substudy 1, all efficacy analyses are presented separately for part A, B and C. For part A data is presented by dose level and overall. For part B, data is presented in separate tables for tumour type by dose level and overall. For part C, data is presented in separate tables for indication by dose level (as applicable at the time). Safety data will be presented as follows:

- Part A only - during dose escalation.
- Part B only (by tumour type)
- Part A+B+C if patients have the same dose and same disease
- Part C only (by indication)

4.2.1 Safety

The Safety and tolerability primary endpoints are assessed in terms of AEs/ Serious Adverse Events (SAEs), AEs leading to discontinuation of AZD8853, DLTs, clinically significant changes from baseline in clinical laboratory parameters, vital signs, and electrocardiogram (ECG) results.

The domain safety also covers exposure and ECOGs.

These variables are collected for all participants. All safety analyses are performed on the safety analysis set. Listings are provided for all participants or the safety analysis set depending on the availability of data.

DLT summaries or listings are provided on the DLT evaluable population set.

4.2.1.1 Exposure

4.2.1.1.1 Definitions and Derivations

Infusion administered medications

Substudy 1:

- Duration of exposure is defined by last date of actual dosing (i.e., a dose > 0 [mg] is given) in the last cycle plus 21 days minus the date of first treatment with IP plus 1 day.
  - For participants who die whilst on study treatment or if a DCO occurs, duration of exposure is defined as date of death/DCO (whichever occurs first) minus the date of first treatment plus 1 day.
  - Therefore: Duration of exposure(days) = (min (last dose date where dose > 0 [mg] + 21 days, date of death, date of DCO) – first dose date + 1).
- The duration of exposure in cycles is calculated as:

  $$\text{Duration of exposure (cycles)} = \text{The number of cycles in which at least one portion of IP was administered (i.e., dose > 0 [mg])}$$

  If a cycle is prolonged due to toxicity, this should still be counted as one cycle.
- The actual duration of exposure is calculated as:

$$\text{Actual duration of exposure (days)} = \text{Number of cycles participants received} \times 21 \text{ (days)}$$

Duration of exposure is calculated as above, and dose interruptions are defined as any length of time where the participant has not taken any of the planned dose in accordance

with the protocol. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

- Dose intensity of IP(s) is addressed by considering relative dose intensity (RDI), where RDI is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. More specifically, RDI is defined as follows:

$$\text{RDI} = 100\,X\,d/D$$

  - where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered if there were no modification to dose or schedule.
- Percentage of first dose received, which is used to define the DLT population is calculated as

$$Percentage\ of\ dosing\ received = \frac{Actual\ first\ dose\ of\ AZD8853\ received}{Planned\ first\ dose\ of\ AZD8853\ received} * 100$$

4.2.1.1.2 Presentation

Duration of exposure to IP in days is summarised by descriptive statistics and by frequency. Dose intensities are summarised by descriptive statistics and by the categories <75, 75-125, and >125. Exposure to IP, i.e., total amount of study drug received, are listed for all participants.

Exposure swimmer plot(s) are produced, with a line presented for each participant to display relevant exposure and disposition details.

Dosing deviations for IP are summarised with reasons for deviations for the following categories: delays and interruptions. The frequency counts and percentage of the number of participants with delays and/or interruptions and total count per participant are summarised. The frequency counts and percentage of the number of participants with dosing delays and total count dose delays per participant are summarised.

4.2.1.2 Adverse Events

MedDRA (using the latest or current version) are used to code the AEs. AEs are graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) (using the CTCAE version referenced in the CSP).

Treatment emergent AEs (TEAEs) are all AEs which onset or worsen in severity following the first administration of IP within the duration of the treatment period, up to and including 97 days [90 days +/- 7 days] after the last dose of IP as per the study safety follow up period

but prior to subsequent cancer therapy. Worsening in severity is determined by comparison with the pre-treatment CTCAE grade of the AE recorded closest to the start of dosing.

For rules on missing or partial dates, see Section 3.3.6. AEs with a missing start time (or where time is not collected) which occur on the same day as first IP administration are reported as treatment emergent SAEs.

When assigning AEs to the relevant phase of the study the following rules apply and any deviations must be agreed by the study team:

- Pre-treatment phase: All AEs with a start date after signing the informed consent form (ICF), prior to the first administration of IP that do not subsequently go on to worsen during the treatment emergent phase.
- Treatment emergent phase: All AEs (starting or worsening) on or after the first dose of study intervention and within 97 days [90 days +/- 7 days] after the last dose of study IP or up to the day prior to start of subsequent therapy, whichever comes first.

SAEs
An SAE is an AE occurring during any study period that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the participant
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs of special interest

An Adverse Event of Special Interest (AESI) is one of scientific and medical interest specific to understanding of the study intervention and may require close monitoring and rapid communication by the investigator to the sponsor. AESIs include but are not limited to:

- CCI [redacted]
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

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

- CCI [redacted])
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

More information regarding AESIs can be found in the CSP section 8.3.6. Other categories may be added, or existing terms may be modified as necessary. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to DBL to ensure any further terms not already included are captured within the categories. Preferred terms used to identify AESI is listed before DBL.

Other Significant Adverse Events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert reviews the list of AEs that were not reported as SAEs and AEs leading to discontinuation of IP. Based on the expert's judgement, AEs of clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory values, vital signs, ECGs, and other safety assessments are performed for identification of OAEs. This review takes place prior to DBL, and any AEs identified are fully documented in meeting minutes. Further review following DBL may result in ad-hoc OAEs being identified, in this case, the OAEs and resulting summaries are fully documented in the CSR.

Examples of these are 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.

4.2.1.2.1 Presentation

All TEAEs are summarised and listed. AEs which are not treatment emergent are listed for the safety analysis set.

TEAEs are counted once for each participant for calculating percentages of participants experiencing TEAE. In addition, if the same TEAE occurs multiple times within a participant, the highest severity, and level of relationship observed are reported. For tables by MedDRA SOC and MedDRA PT, participants with multiple TEAEs are counted once for each SOC/PT.

An overall summary table of the number of participants experiencing each category of AEs is produced. The number of participants experiencing TEAEs by MedDRA SOC and PT are summarised and the severity, and relationship to study drug are summarised. Further splits by CTCAE grade, causal relationship to IP and AEs with Grade 3-5 are also summarised.

Separate tables present DLTs (applicable for Substudy 1 Part A only), AEs leading to discontinuation, SAEs, IP-related AEs, and other significant adverse events.

Details of any deaths are summarised and listed for all participants. SAEs leading to death are also summarised.

SAEs

SAEs are summarised as described above for the TEAEs.

AEs of special interest

Grouped summary tables of certain MedDRA preferred terms are produced and may also show the individual preferred terms which constitute each AESI grouping. Groupings are based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping is provided.

Summaries of the above-mentioned grouped AE categories include number and percentage (%) of participants who have:

- At least one AESI presented by event outcome
- At least one AESI causally related to IP
- At least one AESI leading to discontinuation of IP.

A summary of total duration (days) of AESI is provided for events which have an end date, and this may be supported by summaries of ongoing AESIs at death and, separately, at DCO.

4.2.1.3 Clinical Laboratory, Blood Sample

4.2.1.3.1 Definitions and Derivations

Laboratory tests are grouped according to chemistry, haematology, and coagulation. Laboratory parameters are assessed at baseline as well as throughout the study.

For chemistry, haematology, and coagulant parameters, laboratory abnormalities with toxicity grades according to the NCI CTCAE version 5.0 are derived.

Change from baseline in haematology, clinical chemistry and coagulation endpoints are calculated for each post-dose visit. CTC grade is calculated at each visit. Maximum post-baseline CTC are also calculated. Absolute values are compared to the local laboratory reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low are flagged on the listings.

Liver Function Parameters

Participants with elevated post-baseline Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) or Total Bilirubin that fall into these categories are identified. Number and percentage of these participants are tabulated. The summaries are presented based on categories of the liver function parameters summarised below in Table 5.

Table 5: Liver function parameters

Liver Function Parameters	Category
ALT	• ≥3 × – ≤5 × ULN • >5 × – ≤8 × ULN • >8 × ULN
AST	• ≥3 × – ≤5 × ULN • >5 × – ≤8 × ULN • >8 × ULN
Total bilirubin	• ≥2 × – ≤3 × ULN • >3 × – ≤5 × ULN • >5 × – ≤10 × ULN • >10 × ULN
ALT or AST	• ≥3 × – ≤5 × ULN • >5 × – ≤8 × ULN • >8 × ULN
Potential Hy's law	• (AST ≥ 3 × ULN or ALT ≥ 3 × ULN) and (Total Bilirubin ≥ 2×ULN) [a]

Liver Function Parameters	Category

ALT = Alanine transaminase; AST = Aspartate transaminase; ULN: =upper limit of normal range.

[a] It includes all participants who have ALT or AST≥3xULN and total bilirubin (BILI) ≥2xULN, and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in BILI. Hy's law is potential Hy's law, where no other reason, other than IMP, can be found to explain the combination of increases.

4.2.1.3.2 Presentations

The changes in each laboratory parameter from baseline to each post-baseline visit are summarised graphically.

Laboratory abnormalities occurring from the start of IP administration to the last assessment on study as well as CTC grades are presented in listings together with further information about individual laboratory assessments. Worst toxicity grade, rates of grade 3-4 toxicity, and grade shifts of 2 or more from baseline to the maximum grade are presented. Summaries indicating hyper- and hypo- directionality of change are produced, where appropriate. Laboratory parameters that cannot be graded via NCI CTCAE are summarised with frequencies of post-baseline laboratory values categorized as low (L), normal (N), or high (H) using laboratory normal ranges compared to baseline.

Boxplots may be used to summarize changes in clinical laboratory results at each timepoint if the results are deemed of interest to present.

Chemistry and Haematology clinically significant on-treatment values worse than baseline will be presented. All clinically significant on-treatment values that were originally normal at baseline will be presented. On-treatment clinically significant values that were also clinically significant at baseline will be presented if CTCAE grade is higher than baseline, or if the clinically significant value is a change in direction (i.e. changed from clinically significant low value at baseline to clinically significant high value post baseline).

Listings are provided for all laboratory results.

Liver Function Parameters

Number and percentage of participants with elevated post-baseline ALT, AST or Total Bilirubin are tabulated. Individual participant data where elevated ALT or AST plus total bilirubin fall into the "Potential Hy's law" are summarised and/or listed.

A scatter plot of ALT versus total bilirubin, both expressed as multiples of the upper limit of normal (ULN), will be produced with reference lines at 3×ULN for ALT, and 2×ULN for total bilirubin. The scatter plot will be repeated for AST versus total bilirubin with reference lines at 3×ULN for AST, and 2×ULN for total bilirubin. In each plot, total bilirubin will be in the vertical axis. Liver biochemistry test results over time for patients who show elevated

ALT or AST (≥3xULN) and elevated total bilirubin (≥ 2xULN) (elevated results do not need to be present at the same visit), or a total bilirubin of ≥ 5xULN will be tabulated and plotted.

4.2.1.4 Clinical Laboratory, Urinalysis

4.2.1.4.1 Definitions and Derivations

Laboratory parameters are assessed at baseline as well as throughout the study.

CTC grade is calculated for urinalysis at each visit. Maximum on treatment CTC is also calculated. Absolute values are compared to the local laboratory reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low are flagged in the listings.

4.2.1.4.2 Presentations

For urinalysis, shift from baseline to worst on treatment results are presented. Urinalysis abnormalities occurring from the start of IP administration to the last assessment on treatment are presented.

Urinalysis clinically significant on-treatment values worse than baseline will be presented. All clinically significant on-treatment values that were originally normal at baseline will be presented. On-treatment clinically significant values that were also clinically significant at baseline will be presented if CTCAE grade is higher than baseline.

Listings are provided for urinalysis.

4.2.1.5 Other Laboratory Evaluations

4.2.1.5.1 Definitions and Derivations

Pregnancy testing

Pregnancy tests are obtained at baseline and at day 1 of each cycle.

4.2.1.5.2 Presentations

Pregnancy testing

Any pregnancy tests that result in a positive result are line listed by time-point at which the positive pregnancy result occurred.

4.2.1.6 Vital Signs

4.2.1.6.1 Definitions and Derivations

Vital sign parameters (body temperature, blood pressure, heart [pulse] rate, respiration rate, and body weight) are assessed at baseline and throughout the study.

4.2.1.6.2 Presentations

Vital signs are summarised by study visit which may include descriptive statistics for the value of the parameters and the changes from baseline. Absolute values and change from baseline for vital signs data at each timepoint are presented using box plots.

Listings are also provided for vital signs using the normal ranges in Table 6.

Table 6 Vital Signs Normal Ranges

AZ Test Name	Outside AZ defined reference range lower limit if	Outside AZ defined reference range upper limit if	AZ Unit
Diastolic blood pressure	<40	>110	mm Hg
Pulse	<40	>160	beats/min
Systolic blood pressure	<70	>180	mm Hg
Temperature	<35	>38	° C
Weight	<40	>130	kg

4.2.1.7 Electrocardiogram

4.2.1.7.1 Definitions and Derivations

ECG parameters are assessed at baseline as well as throughout the study. ECG parameters include heart [pulse] rate, RR, PR, QRS, QT and QT interval corrected using Fridericia's formula (QTcF). The QTcF is considered as the primary correction method to assess participant cardiac safety.

ECGs are performed at scheduled timepoints pre-dose and post-dose in single at on treatment visits and in triplicate at SCR and EOT. For triplicate measurements, the mean value of the triplicate measurement are recorded as the value of appropriate timepoint for pre-dose respective post-dose assessment. A triplicate measurement is only deemed missing where all triplicate values are missing, otherwise, if one value is missing the mean is taken from the two obtained measurements, and if two values are missing the value is taken as the one obtained measurement.

From the resting 12-lead ECGs values of the QT and RR intervals, the QTcF is derived using the following formula:

$$QTcF = \frac{QT}{RR^{\frac{1}{3}}}$$

where RR is in seconds.

The values of QTcF (milliseconds) are re-derived from the values of RR and QT during the creation of the reporting database.

The notable ECG interval values while on treatment are:

- Maximum QTcF intervals > 450 milliseconds, > 480 milliseconds, and > 500 milliseconds.
- Maximum changes from baseline in QTcF > 30, >60, and > 90 milliseconds.

4.2.1.7.2 Presentations

ECG parameters are summarised using descriptive statistics by visit and change from baseline in ECG endpoints are calculated for each post-dose visit. Absolute values and change from baseline for ECG data at each timepoint are presented using box plots.

The number and percentage of participants having notable ECG interval values while on treatment are summarised.

Further, QT and QTcF intervals, at any observation on treatment, are summarised.

Listings are also provided for ECGs using the normal ranges in Table 7.

Table 7 ECG Normal Ranges

AZ Test Name	Outside AZ cardiac SKG reference range lower limit if	Outside AZ cardiac SKG reference range upper limit if	AZ Unit
PR	<100	>240	msec
QRS	<70	>120	msec
QT	<300	>450	msec
QTcF	<300	>450*	msec
HR	<45	>120	BPM
RR	<500	>1333	msec

*Cut-off values for categorical analyses recommended by ICH E14
BPM = Beats per minute, Msec = milliseconds

4.2.1.8 Other Safety Assessments

4.2.1.8.1 Definitions and Derivations

Maximum Tolerated Dose Evaluation (applicable to Substudy 1 Part A only)

See Section 6.6.5 of the CSP for the definition of a DLT. For reporting purposes, the DLTs are as approved and documented at the Safety Review Committee meetings.

After the escalation phase is completed, DLT rates at each dose level are estimated by isotonic regression (Ji et al, 2010). The weighted least squares regression model conditional on monotonic non-decreasing DLT rates with increasing dose and use the empirical (observed) DLT rates at each dose level as responses and sample sizes at each dose level as weights, along with the Pool Adjacent Violators Algorithm (PAVA) to estimate the DLT rate at each dose level using available software (eg, Cytel EAST or the function pava from the R package 'ISO'). Given the DLT estimates for each dose level, the MTD is selected from all tried dose levels that have not been previously declared to be unsafe with a "de-escalate to the previous lower dose and the current dose is never used again due to unacceptable toxicity" (DU) decision according to the mTPI-2 decision table. With this constraint, the MTD is determined as the dose level with the DLT estimate closest to the target toxicity level of [redacted]%.

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

If no DLTs are observed meaning the MTD is unable to be concluded, the maximum per protocol dose will be used.

ECOGs

Performance status is assessed according to ECOG criteria at timepoints throughout the study. The ECOG criteria is summarised in section 8.2.2. of the CSP.

4.2.1.8.2 Presentations

Maximum Tolerated Dose Evaluation (applicable to Substudy 1 Part A only)

The MTD evaluation is based on the DLT evaluable population. The number and percentage of participants with DLT during dose escalation are presented by dose level.

ECOGs

The number and percentage of each participant in each ECOG category will be displayed by each timepoint.

4.2.2 Secondary Endpoint: Objective Response Rate

A secondary efficacy endpoint is objective response rate (ORR).

4.2.2.1 Definition

The ORR is programmatically derived based on the site investigator RECIST v1.1 data, and using all scans regardless of whether they were scheduled or not.

Objective Response (OR) is defined as a programmatically derived, confirmed best overall response of Complete Response (CR) or Partial Response (PR) that occurs prior to the initiation of subsequent anticancer treatment and prior to progression. ORR is defined as the percentage of participants with OR.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, are included in the assessment of ORR. Also, only data obtained before the start of subsequent anticancer treatment (excluding radiotherapy) are included. Therefore, both visits contributing to a confirmed response must be prior to progression and prior to subsequent anticancer treatment.

In the case where a participant has two non-consecutive visit responses of PR, then, if the time between the 2 visits of PR is greater than 4 weeks and there is no progressive disease between the PR visits, then a best response of PR is assigned. Similarly, if a participant has visit responses of CR, Not Evaluable (NE), CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR is assigned.

In cases where CRC subjects may undergo potentially curative surgery at some point following treatment, an additional summary of responses will be provided to distinguish between surgically and drug-only induced responses as follow:

- ORR where only responses prior to curative surgery are included in the numerator (secondary endpoint described in previous section).
- ORR where subjects who have surgery that results in the absence of any tumour after surgery are treated as a CR and are included in the numerator.

Subjects receiving surgery should continue to be followed up for objective disease progression as defined by RECIST v1.1.

Overall visit response post curative surgical intervention derivation is described in section 7 Appendices.

4.2.2.2 Derivations

See Section Definition 4.2.2.1.

4.2.2.3 Handling of dropouts and missing data

Handling of missing TL data is described in Appendix A (Section 7.1).

4.2.2.4 Primary Analysis of Secondary Endpoint

ORR is based on a subset of all treated participants with measurable disease at baseline per the site investigator.

Summaries are produced that present the number and percentage of participants with a confirmed tumour response (CR/PR). The ORR is presented with a two-sided 90% CI using the Clopper-Pearson (exact probability) method. Participants that have missing OR assessments at all visits are considered as non-responders and are therefore counted in the denominator of ORR. The main analysis of ORR is based on the response evaluable set.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

Sensitivity analysis is NA.

4.2.2.6 Subgroup Analyses

Subgroup analysis is NA.

4.2.3 Best Overall response

4.2.3.1 Definition

BOR is calculated based on the overall visit responses from each RECIST v1.1 assessment, described in Appendix A (Section 7.1). It is the best response a participant has had following start of IP, but prior to starting any subsequent cancer therapy and up to and including RECIST v1.1 progression or the last evaluable assessment in the absence of RECIST v1.1 progression. Categorization of BOR is based on RECIST v1.1 using the following response categories: CR, PR, Stable Disease (SD); progressive disease; and NE.

BOR is determined programmatically based on RECIST v1.1. using all site investigator data up until the first progression event (i.e., progression or death). For participants whose progression event is death, BOR is calculated based upon all evaluable RECIST v1.1 assessments prior to death.

4.2.3.2 Derivations

For participants who die with no evaluable RECIST v1.1 assessments, if the death occurs ≤ 15 weeks (i.e. 14 weeks [5 weeks + 9 weeks] + 1 week to allow for a late assessment within the assessment window) after first dose of IP, then BOR is assigned to the progressive disease

category. For participants who die with no evaluable RECIST v1.1 assessments, if the death occurs > 15 weeks after first dose then BOR is assigned to the NE category.

For CR/PR, the initial overall visit assessment that showed a response uses the latest of the dates contributing towards a particular overall visit assessment. A participant is classified as a responder if the RECIST v1.1 criteria for a CR or PR are satisfied at any time following first IP dose, prior to RECIST v1.1 progression and prior to starting any subsequent cancer therapy. CR or PR must be confirmed (see detail in Objective Response Section 4.2.2.1).

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment is used. SD should be recorded at least 5 weeks (5 x 7 = 35 days) from first dose.

4.2.3.3 Handling of dropouts and missing data

Handling of missing TL data is described in Appendix A (Section 7.1). Handling of missing subsequent treatment date is described in section 3.3.6.

4.2.3.4 Primary Analysis of Secondary Endpoint

BOR is summarised by the number and percentage of participants for the following categories: CR, PR, SD, PD and NE. No formal statistical analyses are planned for BOR. The main analysis of BOR is based on the Response evaluable set.

4.2.3.5 Sensitivity Analyses

Sensitivity analysis is NA.

4.2.3.6 Subgroup Analyses

Subgroup analysis is NA.

4.2.4 Secondary Endpoint: Disease Control Rate at Study Week 15

DCR at study week 15 is a secondary endpoint.

4.2.4.1 Definition

Disease control is defined as a BOR of confirmed CR or PR or having SD (without subsequent cancer therapy) maintained for ≥ 14 weeks (study week 15) from first IP. Disease control rate at study week 15 weeks (DCR-15) is defined as the percentage of participants who have disease control at study week 15 weeks.

4.2.4.2 Derivations

A programmed derivation for DCR is:

- If participants have a BOR of confirmed CR or PR, they have disease control.

- Or if a participant has SD to at least DCR time point (i.e., duration of SD ≥ DCR time point), they have disease control. (Note participants with unconfirmed responses should be included in this calculation.)
    - Duration of SD is defined as the time from first IP dose until the first documentation of disease progression or death due to any cause, whichever occurs first:
        - Duration of SD (days) = Disease progression or death or PFS censoring date – first IP dose date +1. SD after the start of subsequent cancer therapy should not be included in this duration.
- Otherwise, they do not have disease control.

4.2.4.3 Primary Analysis of Secondary Endpoint

DCR at study week 15 is presented with a two-sided 90% CI using the Clopper-Pearson (exact probability) method. The main analysis of DCR is based on the Response Evaluable population.

4.2.5 Secondary Endpoint: Duration of Response

Duration of Response (DoR) is a secondary endpoint.

4.2.5.1 Definition

DoR is defined as the time from the date of first documented objective response (which is subsequently confirmed) until date of first documented disease progression or death (by any cause in the absence of disease progression).

4.2.5.2 Derivations

$$\text{DoR (Months)} = \frac{(\text{Date of PFS event or censoring-date of first OR that is subsequently confirmed}) + 1}{(\frac{365.25}{12})}$$

where PFS event is progression or death.

The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response is defined as the latest of the dates contributing towards the first visit response of CR or PR (which was subsequently confirmed). If a participant does not progress following a response, then their DoR is censored on the PFS censoring date. Only participants who have achieved OR (confirmed CR or confirmed PR) are evaluated and summarised for DoR.

4.2.5.3 Handling of dropouts and missing data

Handling of missing TL data is described in Appendix A (Section 7.1).

4.2.5.4 Primary Analysis of Secondary Endpoint

Only participants who have achieved objective response (CR or PR) are included in the summaries of DOR. If participant numbers allow (i.e., more than 5 participants are evaluated for DoR), Kaplan-Meier plots of DoR are presented. The median DoR and two-sided 90% CI are estimated using the Kaplan-Meier method. The percentage of participants remaining in response at 3, 6, 9 and 12 months, calculated using the Kaplan-Meier technique, are also presented. Swimmer plots that clearly show the profile of each participant who respond are also produced.

4.2.5.5 Sensitivity Analyses of the Secondary Endpoint

Sensitivity analysis is NA.

4.2.5.6 Subgroup Analyses

Subgroup analyses is defined in section 4.2.2.6

4.2.6 Secondary Endpoint: Progression Free Survival

Progression Free Survival (PFS) is a secondary endpoint.

4.2.6.1 Definition

The PFS is defined as the time from first dose of IP until the date of first documented 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.

4.2.6.2 Derivations

$$\text{PFS (Months)} = \frac{(\text{Date of PFS event or censoring-date of first dose of IP}) + 1}{(\frac{365.25}{12})}$$

where PFS event is progression or death.

Participants who have not progressed or died at the time of analysis are censored at the time of the latest date of assessment from their last evaluable disease assessment. However, if the participant progresses or dies immediately after two or more consecutive missed visits, the participant is censored at the time of the latest evaluable disease assessment prior to the two missed visits. Note: a NE visit is not considered as a missed visit.

Given the scheduled visit assessment scheme (i.e., first visit at week six, then nine-weekly for till 52 weeks then twelve-weekly thereafter) the definition of 2 missed visits changes.

If the previous RECIST v1.1 assessment is less than study day 288 (i.e. study week 42) and greater than study day 99 (study week 15), then two missed visits equates to 20 weeks since

the previous RECIST v1.1 assessment, allowing for early and late visits (i.e. 2 x 9 weeks + 1 week for an early assessment + 1 week for a late assessment = 20 weeks).

If the previous RECIST visit is after the visit assessment at study week 6 or study week 15, then two missed visits equate to:

- 15 weeks (105 days), if study week 6 (5 weeks after 1st IP dose) and study week 15 (14 weeks after 1st IP dose) are the two consecutive visits missed [(1 x 5 weeks) + (1 x 9 weeks) + 1 week for late assessment].
- 19 weeks (133 days), if study week 15 (14 weeks after 1st IP dose) and week 24 (23 weeks after 1st IP dose) are the two consecutive visits missed [(1 x 9 weeks) + (1 x 9 weeks) + 1 week for late assessment].

If the two missed visits occur over the period when the scheduled frequency of RECIST v1.1 assessments changes from nine-weekly to twelve-weekly this equates to 23 weeks (i.e. take the average of 9 and 12 weeks which gives 10.5 weeks and then apply same rationale, hence 2 x 10.5 weeks + 1 week for an early assessment + 1 week for a late assessment = 23 weeks). The time period for the previous RECIST v1.1 assessment is from study days 288 to 351 (i.e., study week 42 to study week 51).

From study day 351 (study week 51 onwards [when the scheduling changes to twelve-weekly assessments]), two missed visits equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks). This is also summarised in the Table 8 below.

Where study day, is the number of days on the study, in which Cycle 1 Day 1 is taken as study day 1.

Table 8: Two missed visits rule for PFS for schedule changes

Scheduled Assessment	Previous RECIST assessment	Two missed RECIST visits window
5 weeks up to study week 6 then Q9 till study week 52	No evaluable RECIST visits or no baseline RECIST scan	(1 x 5 weeks) + (1 x 9 weeks) + 1 week = 15 weeks (105 days)
5 weeks up to study week 6 then Q9 till study week 52	Baseline	(1 x 5 weeks) + (1 x 9 weeks) + 1 = 15 weeks (105 days)
5 weeks up to study week 6 then Q9 till study week 52	Study day 36 (Study week 6)	2 x 9 weeks + 1 week = 19 weeks (133 days)
Q9W till study week 52	>Study day 99– Study day 288 (From study week 15 up to study week 42)	2 x 9 weeks + 2 weeks = 20 weeks (140 days)
	>Study day 288 – Study day 351 (Study week 42 – Study week 51) (change period from Q9W to Q12W)	2 x [(9 weeks+12 weeks)/2] + 2 weeks = 23 weeks (161 days)
Q12W thereafter	>Study Day 351 onwards	2 x 12 weeks + 2 weeks

RECIST = Response Evaluation Criteria in Solid Tumours v1.1;

If the participant has no evaluable disease assessments post-baseline or does not have baseline tumour assessment data, they are censored at Day 1 unless they die within two visits of first IP dose (14 weeks plus 1 week allowing for a late assessment within the visit window) then the death date qualifies as a PFS event.

A summary of censoring rules and the date of progressive disease/death or censoring are given in Table 9. Note that censoring overrides event in certain specified cases and the table below does not indicate the order for programming.

Table 9: Summary of Censoring Rules for PFS

Situation	Date of progressive disease /Death or Censoring	PFS Outcome
Documented Progressive Disease or death in the absence of progression	Date of earliest documentation of progressive disease or date of death in the absence of progression	Event
Either no tumour assessment at baseline or no evaluable assessments post-baseline AND death prior to second scheduled post-baseline disease assessment	Date of death	Event
Either no tumour assessment at baseline or no evaluable assessments post-baseline AND no death prior to second scheduled post-baseline disease assessment	Date of first dose (Day 1)	Censored
Progressive disease or death (in the absence of progression) immediately after ≥ 2 consecutive missed disease assessments as per the protocol specified assessment schedule	Last evaluable progression-free disease assessment prior to missed assessments (if available). Otherwise, the date of censoring is Date of first dose (Day 1)	Censored
On-going with neither progressive disease nor death at the time of analysis or lost to follow-up or withdrawn consent	Date of last evaluable disease assessment	Censored

PFS = progression-free survival

The PFS time is always derived based on scan/assessment dates, and not on visit dates.

RECIST v1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

- The date of progression is determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a participant for PFS the participant is censored at the latest of the dates contributing to a particular overall visit assessment.

Note: for TLs only the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

The number of participants alive and progression free at 3, 6, 9 and 12 months (PFS-3, PFS-6, PFS-9, and PFS-12) is defined as the Kaplan-Meier estimate of PFS at 3, 6, 9 and 12 months.

'Potential' duration of follow-up for PFS is applicable only for PFS censored participants and is defined as follows:

$$\text{Potential duration of follow up for PFS (Months)} = \frac{(\text{Date of PFS censoring-date of first dose of IP})+1}{(\frac{365.25}{12})}$$

4.2.6.3 Handling of dropouts and Missing Data

See section 4.2.6.2.

4.2.6.4 Analysis of the Secondary Endpoint

The main analysis of PFS is based on the safety analysis set. The number and percentage of participants experiencing a PFS event broken down by type of event/censoring and Kaplan-Meier plots of PFS are presented. The median PFS and its two-sided 90% CI are estimated using the Kaplan-Meier method if participant numbers allow.

The treatment status at progression of participants at the time of analysis are summarised. This includes;

- The number (%) of participants who were on treatment at the time of progression
- The number (%) of participants who discontinued IP prior to progression
- The number (%) of participants who have not progressed and were on treatment or discontinued treatment.

A summary of the duration of follow-up for PFS is included using median (range). This is presented for censored participants (including all types of PFS censoring).

The proportion of participants alive and progression free at 3, 6, 9 and 12 months and associated two-sided 90% CI are estimated using the Kaplan-Meier method.

4.2.7 Secondary Endpoint: Change in Target Lesion Tumour Size

Change in TL tumor size is a secondary endpoint.

4.2.7.1 Definition

This is based on RECIST v1.1 TL measurements taken at baseline and each post-baseline assessment. Tumour size is the sum of the longest diameters (or short axis measurements for

lymph nodes) of the TLs. Baseline for RECIST v1.1 is defined to be the last evaluable assessment prior to first IP dose.

An outcome endpoint for this study is percentage change from baseline in TL tumour size at each post-baseline assessment e.g., at Study week 15.

The tumour size and percentage change from baseline in the sum of tumour size at each assessment are calculated. The best change in tumour size from baseline (i.e., depth of response) is the largest decrease from baseline or the smallest increase from baseline in the absence of a reduction and includes all assessments:

- up to and including the first visit at which the overall visit response is progressive disease,
- prior to death in the absence of progression,
- prior to the start of subsequent anti-cancer therapy (including radiotherapy)
- or up to and including the last evaluable RECIST v1.1 assessment if the participant has not died, progressed, or started subsequent anti-cancer therapy.

Each post-baseline disease assessment for a participant that meets the following conditions are included: all TLs identified at baseline have measurements recorded at the current visit (i.e., they cannot be not done or not evaluable). If a lesion is recorded as <=5mm then this is used in the calculations.

4.2.7.2 Derivations

For visit based summaries, whenever TL tumour size data for each post-baseline assessment (note: or visit at which progression was documented if before the post-line visit) is available then this is used in the analysis. A windowing rule is applied and follows the protocol allowed visit window; therefore, any RECIST v1.1 scan performed within Study W6(D1-D7), W15(D1-D7), W24±6D then Q9W±6D until W52, then Q12W±6D of the protocol scheduled visit is used for that visit.

The percentage change from baseline in TL tumour size at each post-baseline assessment is obtained for each participant taking the difference between the sum of the TLs at each post-baseline assessment and the sum of the TLs at baseline divided by the sum of the TLs at baseline times 100. For example, the percentage change from baseline in TL tumour size for the post-baseline visit at study week 15 is calculated as follows:

$$\text{Percentage change from baseline in TL tumour size} = \frac{(\text{Study Week 15 - Baseline})}{(\text{Baseline})} \times 100$$

For best percentage change, if it cannot be calculated due to missing data (including if the participant has no TLs at baseline), a value of +20% is imputed as the best percentage change from baseline in the following situations (otherwise best percentage change is left as missing):

- If a participant has no post-baseline assessment and has died;
- If a participant has new lesions or progression of NTLs or TLs;
- If a participant has withdrawn due to progressive disease and has no evaluable TL data before or at progressive disease.

For the outcome endpoint percentage change from baseline in TL tumour size at each post-baseline assessment i.e., Study week 15, participants who progress before study week 15 should have had a tumour assessment performed at the time of progression prior to treatment discontinuation. The tumour size from their latest progression assessment is used instead of the study week 15 assessment for these participants.

4.2.7.3 Primary Analysis of Secondary Endpoint

Only participants with measurable disease at baseline are included in summaries of change in tumour size (measurable disease is as denoted on the eCRF by the investigator).

The TL tumour size and percentage change in TL tumour size from baseline is summarised using descriptive statistics and presented at each timepoint.

The median best percentage change from baseline and other summary statistics are presented, together with the number of participants. The median percentage change from baseline at each post baseline assessment timepoint and other summary statistics are presented, together with the number of participants.

The best percentage change from baseline in tumour size is presented graphically using waterfall plots, with the bars ordered from the largest increase to the largest decrease. Separate waterfall plots are used to present each participant's best percentage change in TL tumour size as a separate bar. A reference line at the –30% change in TL tumour size level is added to the plots, which corresponds with the definition of 'partial response'. All progressions are marked with a '●' or designated with patterns or colors for ORR categories. Flagged progressions on the percentage change in TL tumour size at a particular timepoint are based upon NTL or new lesion progression at that timepoint and flagged progressions on the best percentage change will be based upon NTL or new lesion progression at the same timepoint as the best percentage change. The scale in these plots are fixed to be from -100 to 100 to avoid presenting extreme values. Values that are capped as a result of this restriction to the scale are marked with '#'. Values are ordered in descending order with the imputations due to death appearing first followed by a gap followed by all other participants.

Additionally, 'spider' plots of percentage change from baseline in TL size by participant are presented. This depicts each participant's percentage change from baseline in TL tumour size as a line over time and progression due to non- target and/or new lesions are indicated.

4.2.8 Secondary Endpoint: Overall Survival

Overall Survival (OS) is a secondary efficacy endpoint.

4.2.8.1 Definition

Overall survival is defined as the time from the date of first IP dose until death due to any cause regardless of whether the participant withdraws from study therapy or receives another anti-cancer therapy.

4.2.8.2 Derivations

$$\text{OS (Months)} = \frac{(\text{Date of death or censoring-date of first dose of IP}) + 1}{(\frac{365.25}{12})}$$

Any participant not known to have died at the time of analysis is censored based on the last recorded date on which the participant was known to be alive.

Note: For any OS analysis performed (prior to the final OS analysis), in the absence of survival calls being made, it may be necessary to use all relevant eCRF fields to determine the last recorded date on which the participant was known to be alive for those participants still on treatment (since the SURVIVE module is only completed for participants off treatment if a survival sweep is not performed). The last date for each individual participant is defined as the latest among the following dates recorded on the eCRFs:

- AE start, stop and change in severity dates
- Admission and discharge dates of hospitalization
- Physical examination, ECOG and ECG dates
- IP Treatment administration dates
- End of treatment date
- Concomitant medication start and stop dates
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on RECIST v1.1 eCRF

- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status eCRF
- End of study date

The proportion of participants alive at 3, 6, 9 and 12 months (OS-3, OS-6, OS-9, OS12) is defined as the Kaplan-Meier estimate of OS at 3, 6, 9, and 12 months.

Duration of follow-up for OS is reported separately for censored participants and non-censored participants and is defined as follows:

$$\text{Duration of follow up for OS (Months)} = \frac{(\text{Date of death or censoring (date last known to be alive)-date of first dose of IP})+1}{(\frac{365.25}{12})}$$

4.2.8.3 Handling of dropouts and missing data

If a participant is known to have died where only a partial death date is available, then the date of death is imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- For Missing day only – using the 1st of the month.
- For Missing day and Month – using the 1st of January.

If there is evidence of death but the date is entirely missing, it is treated as missing, i.e. censored at the last known alive date.

4.2.8.4 Primary Analysis of Secondary Endpoint

The analysis of OS is based on the safety population. The number and percentage of participants experiencing an OS event and Kaplan-Meier plots of OS are presented. The median OS and two-sided 90% CI are estimated using the Kaplan-Meier method if participant numbers allow. Summaries of the number and percentage of participants who have died, those still in survival follow-up, those lost to follow-up and those who have withdrawn consent are provided.

The proportion of participants alive at 3, 6, 9 and 12 months (OS-3, OS-6, OS-9, and OS-12) and associated two-sided 90% CI are estimated using the Kaplan-Meier method.

A summary of the duration of follow-up for OS is included using median (range). This is presented separately for censored and non-censored participants.

4.2.8.5 Sensitivity Analyses of the secondary endpoint

Sensitivity analysis is NA.

4.2.8.6 Supplementary Analyses of the secondary endpoint

Supplementary analysis is NA.

4.2.8.7 Subgroup analyses

Subgroup analyses is defined in section 4.2.2.6

4.2.9 Secondary Endpoint: Changes in ctDNA from baseline

Changes in CtDNA from baseline is a secondary endpoint.

4.2.9.1 Definition and Derivations

Change in ctDNA is defined as the percentage change in ctDNA from baseline to each timepoint for the safety population.

4.2.9.2 Derivations

Percentage change in ctDNA from baseline to each post baseline timepoint as well as the maximum change are analyzed descriptively on the Safety Population.

4.2.9.3 Primary Analysis of Secondary Endpoint

Percentage change from ctDNA from baseline to each timepoint is summarised by mean percentage change and St.Dev. Maximum change is also summaries by mean and St.Dev.

4.2.10 Secondary Endpoint: Change in circulating GDF15 serum levels (Applicable for Substudy 1: Part A and Part B only)

4.2.10.1 Definition and Derivations

Changes in free GDF15 serum levels is defined as change in GDF15 serum levels from pre-treatment (baseline) to each post baseline timepoint on the PD population.

4.2.10.2 Primary Analysis of Secondary Endpoint

The change in circulating free GDF15 serum levels from pre-treatment (baseline) to each post baseline timepoint, will be summarised using descriptive statistics. Standard summary statistics n, mean, St. Dev, median, minimum, and maximum will be presented. Summary of absolute values and percent change from baseline will be produced by cohort by visit.

Listing of individual values is provided.

Boxplot may be produced to represent the evolution of GDF15 over time. If a group has ≤ 10 patients, line plot will be produced instead of boxplot.

4.2.11 Secondary Endpoint: Change in CD8 tumour infiltration by IHC using baseline and on treatment samples (Applicable for Substudy 1: Part A and B only)

4.2.11.1 Definition and Derivations

Changes in CD8 tumour infiltration by IHC are defined as change in CD8 tumour infiltration by IHC from pre-treatment (baseline) from on treatment fresh biopsies (C2D8 +/- 5 days) on the PD population.

Tissue obtained as part of mandatory paired biopsies obtained before and during treatment (Screening [Day -28 to -1], C2D1 and C2D8) will be assessed for CD8+ T cell tumour infiltration.

4.2.11.2 Primary Analysis of Secondary Endpoint

The change in CD8 tumour infiltration measured by IHC will be summarised using descriptive statistics, standard summary statistics n, mean, St. Dev, median, minimum, and maximum will be presented.

Summary of absolute values and percent change from baseline will be produced.

Listing of individual values is provided.

4.2.12 Pharmacokinetics

This section covers details related to PK endpoints and analyses.

The (PK) parameters of the concentration data for AZD8853 and its metabolites (if metabolite[s] are defined and their concentrations are available) are derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara) by Clinical Pharmacology and Marketed Products at AstraZeneca

Plasma PK Parameters

PK analysis is, where data allow, carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist with approval from the AZ Clinical Pharmacology Scientist (CPS). Nominal sampling times may be used for any agreed interim PK parameter calculations.

For each PK sampling period, plasma concentrations that are non-quantifiable (NQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration is set to a value of zero. After this time point, NQ plasma concentrations are set to missing for all concentration profiles. Where 2 or more consecutive concentrations are NQ at the end of a

profile, the profile is deemed to have terminated and therefore any further quantifiable concentrations are set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile is excluded from the PK analysis.

Cmax, Cmin, tmax, tlag and tlast are taken directly from the concentration-time profiles.

Refer to Appendix B (Section 7.2) for the calculation of PK parameters including λz, Area under the curve (AUCs), Clearance (CL), Accumulation ratio (Rac), Temporal Change Parameter (TCP), and so on.

For each analyte, plasma concentrations for each scheduled time-point are summarised by Study Part, PK Day/Visit and Treatment dose level using appropriate descriptive statistics. Similar data (e.g., single dose or multiple doses for the same dosing regimen) from different Study Parts or PK Days/Visits may also be summarised together. Individual concentrations with time deviations of greater than ±10% from the protocol scheduled time, are used in the PK analysis but are flagged for exclusion from the summary tables and corresponding figures.

The following descriptive statistics are presented for plasma concentrations:

- n
- n below Lower limit of quantification (LLOQ)
- geometric mean (gmean)
- geometric coefficient of variance (%) (gCV)
- arithmetic mean (mean)
- arithmetic standard deviation (Std Dev)
- median
- minimum (min)
- maximum (max)
-

The gmean is calculated as:

$$\exp(\mu)$$

where μ is the mean of the data on the natural log scale.

The gCV is calculated as:

$$100 \times \sqrt{[\exp(\sigma) - 1]}$$

where σ is the Std Dev of the data on the natural log scale.

Where required for plots: The gSD is calculated as:

$$\exp(\sigma)$$

where σ is the Std Dev of the data on the natural log scale.

The gmean ± gSD (gmean-gSD and gmean+gSD) are calculated as:

$$\exp[\mu \pm \sigma]$$

Protocol scheduled times are used to present the PK concentration summary tables and corresponding gmean concentration-time figures.

Handling of Non-Quantifiable Concentrations

Individual concentrations below the LLOQ of the bioanalytical assay are reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable are reported as NR and those that are missing are reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS are handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS are excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean and gCV% are set to Not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics are calculated for that time point. The gmean, minimum, median and maximum are reported as NQ and the gCV% as NC.
- The number of values below LLOQ (n < LLOQ) are reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration or PK parameter (e.g. Cmax, Cmin, Clast) to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

PK parameter Listings

All reportable PK parameters, including individual diagnostic and lambda z related parameters, are listed for each participant by Study Part, PK Day/Visit and Treatment, for each analyte separately.

PK parameter descriptive statistics

All primary and secondary PK parameters are summarised for each analyte by Study Part, PK Day/Visit and Treatment dose using appropriate descriptive statistics. Similar parameter data (e.g., single dose or multiple doses for the same dosing regimen) from different Study Parts or PK Days/Visits may also be summarised together.

The descriptive statistics for PK parameters are presented as follows:

- Cmax, Cmin, Clast, AUC(0-t), AUCinf, AUCτ, AUClast: present n, gmean, arithmetic mean of non log-transformed data (mean), arithmetic standard deviation (Std Dev), gCV(%), median, min and max.
- t½λz, CL, Vss, MRT, : present n, arithmetic mean of non log-transformed data (mean), arithmetic standard deviation (Std Dev), median, min and max.
- Cmax/D, AUCinf/D, AUC(0-t)/D, AUCτ/D , AUClast/D, λz, and all parameter ratios (e.g Rac, TCP, peak:trough ratio and fed to fasted ratios): present n, gmean, gCV(%), mean, Std Dev, median, min and max.
- tmax, tlag, and tlast: present n, median, min and max.
- Diagnostic parameters (e.g. t upper, t lower, n obs, Rsq adj and AUCextr): present n, arithmetic mean, Std Dev, gmean, gCV%, median, min and max.

Three values are required as a minimum for PK parameters to be summarised. Two values are presented as a min and max with the other summary statistics as NC.

If one or more values for a given parameter is zero, then no geometric statistics are calculated for that parameter and the results for geometric statistics are set to NA (Not Applicable).

Graphical presentation of PK data

All mean (arithmetic mean and/or gmean) plots or combined plots showing all participants by treatment are based on the PK analysis set. Individual plots by participant are based on the safety analysis set. Scatter plots for individual PK parameters versus Treatment dose present both summary parameter data and individual participant parameter data for each Treatment dose including only participants in the PK analysis set.

For consistency, the plasma concentration values used in the mean (arithmetic mean and/or gmean) data graphs are those given in the descriptive statistics summary table for each time point.

For gmean concentration-time plots, NQ values are handled as described for the descriptive statistics; if the geometric mean is NQ, the value plotted is zero for linear plots and missing for semi-logarithmic plots. Any gmean±gSD error bar values that are negative are truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

For individual plots, plasma concentrations which are NQ prior to the first quantifiable concentration are set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations are regarded as missing.

Data permitting, the following figures are presented as appropriate:

- Figures for the mean (arithmetic mean and/or gmean) plasma concentration-time data (with ±Std Dev and/or ±gSD error bars) presented on both linear and semi-logarithmic scales using scheduled post-dose time as follows:
  - By PK Day for each analyte with all or selected single dose Treatments (e.g., dose level) overlaid on the same plot and/or all or selected multiple dose Treatments (e.g., dose levels and schedule) overlaid on the same plot
  - By PK Treatment for each analyte with all or selected single dose PK days and all or selected multiple doses PK Days overlaid on the same plot
  - By PK Treatment with all or selected single dose PK days for each analyte overlaid on the same plot and/or all or selected multiple doses PK Days for each analyte overlaid on the same plot

- Individual participant plasma concentration-time data graphically presented on both linear and semi-logarithmic scales using actual time post-dose as:
  - By participant with all and/or selected PK Days for the same participant overlaid on the same plot
  - Combined individual plots with all participants overlaid on the same plot for each single dose Treatment (e.g., dose level) and/or each multiple dose Treatment (e.g., dose level and schedule)

- Individual and summary single dose and/or multiple dose PK parameter data graphically presented on scatter plots of the PK parameter value

- Individual and summary single dose and/or multiple dose PK parameter data graphically presented as line plots of the PK parameter value against treatment with each individual and the mean value joined with a line between the treatment

- Ratios of a single dose and/or multiple dose PK parameter value for one Treatment (e.g., in combination with another drug or under fed conditions) divided by the value for another Treatment (e.g., not in combination with the other drug or under fasted conditions respectively) plotted against each individual participant or against each Treatment

- Scatter plot of pharmacokinetic parameters (Cmax, AUCinf and AUC(0-t)) versus dose presented on logarithmic scales

Precision and Rounding Rules for Pharmacokinetic Data

PK concentration data

PK concentration data listings present to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

PK concentration descriptive statistics present 4 significant figures with the exception of the min and max which present 3 significant figures and n and n<LLOQ which present as integers.

PK parameter data

PK parameter listings are presented according to the following rules:

- Cmax, Cmin and Clast: present to the same number of significant figures as received from the bioanalytical laboratory

- tmax, tlast, tlag, t lower and t upper: present as received in the data, usually to 2 decimal places

- AUCinf, AUC(0-t), AUCτ, AUClast, AUC/D, AUC(0-t)/D, AUCτ/D, AUClast/D, AUCextr, λz, t½λz, CL,MRT, Vss, Vz, all ratios of PK parameters (e.g. Rac, TCP, Peak:Trough ratio), Rsq adj, : present to 3 significant figures

- F and Frel: present to 2 decimal places

- n obs: present as an integer (no decimals)

The descriptive statistics for PK parameter data are presented to 4 significant figures with the exception of the min and max which are presented to 3 significant figures apart from the following:

- λz: present to 5 significant figures with min and max to 3 significant figures

- tmax, tlag, and tlast: present as received in the data, usually to 2 decimal places
- number of values (n): present as an integer

4.2.13 Immunogenicity

A summary of immunogenicity results is provided showing the number and percentage of participants who develop detectable Anti-Drug Antibodies (ADAs) against AZD8853, based on the participants in the immunogenicity analysis set. The number of ADA evaluable patients in the treatment group is used as the denominator for percentage calculation. Participants and/or data excluded from the immunogenicity analysis set are presented in separate outputs.

The following categories are included in the summary table:

- ADA positive at baseline and/or post-baseline visits. The percentage of these participants in a population is known as ADA prevalence.
- Treatment-induced ADA positive (positive post-baseline and not detected at baseline).
- Treatment-boosted ADA positive (baseline ADA titer that was boosted greater than the variability of the assay (i.e., ≥ 4-fold increase)
- Treatment-emergent ADA positive (either treatment-induced ADA positive or treatment-boosted ADA positive). The percentage of these participants in a population is known as ADA incidence.
- ADA positive post-baseline and positive at baseline.
- ADA positive at baseline and not detected post-baseline.
- Persistent positive, defined as ADA negative at baseline and having at least 2 post-baseline ADA positive measurements with ≥ 16 weeks between first and last positive, or an ADA positive result at the last available post baseline assessment.
- Transient positive, defined as ADA negative at baseline and at least one post- baseline ADA positive measurement and not fulfilling the conditions for persistently positive.

Blood samples collected outside of the scheduled time window are summarized at the next nominal time point if that does not already have a value, otherwise it is presented in listings with data excluded from summary outputs.

ADA results will also be listed for participants included in the immunogenicity analysis set.

5 INTERIM ANALYSIS

Substudy 1

In the efficacy expansions (Part C1 and Part C2) an interim analysis is performed after the 20th participant in each expansion has had the opportunity for 2 on-treatment RECIST v1.1 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 [redacted]

6 REFERENCES

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7 APPENDICES

7.1 Appendix A RECIST

Derivation of RECIST v1.1 Visit Responses

For all participants, the RECIST v1.1 tumour response data is used to determine each participant's visit response according to RECIST version 1.1. It is also used to determine if and when a participant has progressed in accordance with RECIST version 1.1 and their best objective response to IP.

Baseline radiological tumour assessments are performed no more than *28* days before the start of IP and ideally as close as possible to the start of IP Tumour assessments are performed 6 weeks after 1st IP then every 9 weeks, until week 52 then every 12 weeks until disease progression.

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

From the investigator's review of the imaging scans, the RECIST v1.1 tumour response data is used to determine each participant's visit response according to RECIST version 1.1. At each visit, participants are programmatically assigned a RECIST version 1.1 visit response of CR, PR, SD, or Progressive Disease, using the information from TLs, NTLs and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a participant has had a tumour assessment that cannot be evaluated, then the participant is assigned a visit response of NE (unless there is evidence of progression in which case the response is assigned as Progressive Disease).

Please refer to Table 10 for the definitions of CR, PR, SD and Progressive Disease.

RECIST v1.1 outcomes (i.e. PFS, ORR etc.) are calculated programmatically for the site investigator data (see last section of this Appendix) from the overall visit responses.

Target Lesions (TLs) – site investigator data

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A participant can have a maximum of five measurable lesions recorded at baseline with a maximum of two lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as TLs. If more than one baseline scan is recorded, then measurements from the one that is closest and prior to first IP dose is used to define the baseline sum of TLs. It is the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In which circumstance the next largest lesion, which can be measured reproducibly, is selected.

All other lesions (or sites of disease) not recorded as TL are identified as NTLs at baseline. Measurements are not required for these lesions, but their status are followed at subsequent visits.

Note: For participants who do not have measurable disease at entry (i.e. no TLs) but have non-measurable disease, evaluation of overall visit responses are based on the overall NTL assessment and the absence/presence of new lesions (see section below for further details). If a participant does not have measurable disease at baseline, then the TL visit response is Not Applicable (NA).

Table 10: TL Visit Responses (RECIST v1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for progressive disease are not met.
Progressive disease	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
Not evaluable (NE)	Only relevant in certain situations (i.e. if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not Applicable (NA)	No TLs are recorded at baseline.

CR = Complete Response; NA = Not Applicable; NE = Not Evaluable; PR = Partial Response; SD = Stable Disease; TL = target lesion.

Rounding of TL data

For calculation of progressive disease and PR for TLs percentage changes from baseline and previous minimum are rounded to one decimal place before assigning a TL response. For example, 19.95% is rounded to 20.0% but 19.94% is rounded to 19.9%

Missing TL data

For a visit to be evaluable then all TL measurements are recorded. However, a visit response of progressive disease is still assigned if any of the following occurred

- A new lesion is recorded,
- An NTL visit response of progressive disease is recorded,

- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared.

Note: the nadir can only be taken from assessments where all the TLs had a LD recorded.

If the TL visit response is not recorded as progressive disease, then the TL visit response is NE.

If there is at least one TL measurement missing and a visit response of progressive disease cannot be assigned, the visit response is NE.

If all TL measurements are missing, then the TL visit response is NE. Overall visit response is also NE, unless there is a progression of non-TLs or new lesions, in which case the response is progressive disease.

Lymph nodes
For lymph nodes, if the size reduces to < 10mm then these are considered non-pathological. However, a size is still given, and this size is still used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10mm and all other TLs are 0mm then although the sum may be > 0mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR
Only CR, progressive disease or NE can follow a CR. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response is set to CR irrespective of whether the criteria for progressive disease of TL is also met i.e. if a lymph node short axis increases by 20% but remains < 10mm.

- If some lesion measurements are missing but all other lesions meet the CR criteria (i.e., 0mm or < 10mm for lymph nodes) then response is set to NE irrespective of whether the criteria for progressive disease of TL is also met i.e. if a lymph node short axis increases by 20% but remains < 10mm.

- If not all lesions are missing, and those that are non-missing do not meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis ≥ 10mm or the reappearance of previously disappeared lesion), then response is set to progressive disease.

- If all lesions are missing the response is set to NE.

TL too big to measure
If a TL becomes too big to measure this is indicated in the database and a size ('*x*') above which it cannot be accurately measured is recorded. If using a value of *x* in the calculation

of TL response does not give an overall visit response of progressive disease, then this is flagged and reviewed by the study team. It is expected that a visit response of progressive disease remains in the vast majority of cases.

TL too small to measure
If a TL becomes too small to measure, then this is indicated as such on the case report form and a value of 5mm is entered into the database and used in TL calculations. However, a smaller value is used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response of progressive disease results (at a subsequent visit) then this is reviewed by the study team blinded to treatment assignment.

Irradiated lesions/lesion intervention
Previously irradiated lesions (i.e., lesion irradiated prior to entry into the study) are recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization but note this does not include protocol specified biopsies), are handled in the following way. Once a lesion has had intervention then it is treated as having intervention for the remainder of the study noting that an intervention most likely shrinks the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) are summed and the calculation is performed in the usual manner. If the visit response is progressive disease, this remains as a valid response category.
- Step 2: If there is no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing. If progressive disease has not been assigned, then the visit response is set as NE.

At subsequent visits, the above steps are repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention are treated as missing.

Lesions that split in two
If a TL splits in two, then the LDs of the split lesions are summed and reported as the LD for the lesion that split.

Lesions that merge
If two TLs merge, then the LD of the merged lesion are recorded for one of the TL sizes and the other TL size is recorded as 0mm.

Change in method of assessment of TLs

Computerised tomography (CT), magnetic resonance imaging (MRI) and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. If a change in method of assessment occurs, between CT and MRI this is considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g., CT changes to clinical examination or vice versa), any affected lesions are treated as missing.

Non-target lesions (NTLs) and new lesions – site investigator data.

At each visit, the investigator is to record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

NTL response is derived based on the investigator's overall assessment of NTLs as follows in Table 11.

Table 11: NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive disease	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non progressive disease	Persistence of one or more NTLs with no evidence of progression.
Not evaluable (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.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline.

CR = Complete Response; NA = Not Applicable; NE = Not Evaluable; NTL = non-target lesion; TL= target lesion.

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 the presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions are also recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and indicates disease progression.

The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

New lesions are identified via a Yes/No tick box. The absence and presence of new lesions at each visit are listed alongside the TL and NTL visit responses.

A new lesion indicates progression, so the overall visit response is progressive disease irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank, this is not evidence that no new lesions are present but should not overtly affect the derivation.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and is not included in any assessment of NTLs.

Participants with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

Overall visit response – site investigator data

Table 12 defines how the previously defined TL and NTL visit responses are combined with new lesion information to give an overall visit response.

Table 12: Overall visit responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-progressive disease or NE	No (or NE)	**PR**
PR	Non- progressive disease or NE or NA	No (or NE)	**PR**
SD	Non- progressive disease or NE or NA	No (or NE)	**SD**
Progressive Disease	Any	Any	**Progressive Disease**
Any	Progressive Disease	Any	**Progressive Disease**
Any	Any	Yes	**Progressive Disease**
NE	Non- progressive disease or NE or NA	No (or NE)	**NE**
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-progressive disease	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**
NA	NA	No (or NE)	**NED**

CR = Complete Response; NA = Not Applicable; NE = Not Evaluable; NED = No evidence of disease; PR = Partial Response; SD = Stable Disease.

Following curative surgical intervention, each subject's TL visit response will be captured and assigned as previously outlined in section 7.1.

NTL visit response will be derived based on the Investigator's overall assessment of NTLs and the overall visit response will be derived as follows in Table 13.

Table 13: Overall visit responses post curative surgical intervention*

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR, NE (or NA)	No (or NE)	**CR**
CR or NA	CR, NE (or NA)	Yes	**Progressive Disease**
NA	CR or NE	No (or NE)	**CR**

CR = Complete Response; NA = Not Applicable; NE = Not Evaluable; PR = Partial Response; SD = Stable Disease.

* It is assumed that if the subject's disease burden has reduced enough in response to therapy to enable surgery, then those subjects should be regarded as having a CR (assuming all evidence of disease is removed).
Curative surgical interventions will be identified from the **Subsequent Cancer therapy** (**CAPRX2**) form and the data will be reviewed case-by-case by the study team for confirmation.

7.2 Appendix B PK Parameter Derivation

Pharmacokinetic parameter definitions and derivations are described in Table 14 below.

Table 14: Pharmacokinetic parameter definitions and derivations

Parameter Symbol (used in CSP/SAP/ CSR)	Definition	Derivation
AUC(t1-t2)	Partial area under the plasma concentration-time curve from time t1 to time t2	Using the linear up/log down trapezoidal rule
AUCτ	Area under plasma concentration-time curve in the dose interval	Using the linear up/log down trapezoidal rule
AUCinf	Area under plasma concentration-time curve from zero to infinity	Calculated by AUC(0-t) and then extrapolated by Clast/λz to infinity
AUClast	Area under plasma concentration-time curve from zero to the last quantifiable concentration	Using the linear up/log down trapezoidal rule
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf	
AUMCinf	Area Under the first Moment Curve from time 0 to infinity	Using the linear up/log down trapezoidal rule
AUMClast	Area Under the first Moment Curve from time 0 to the time of the last quantifiable concentration (at tlast)	Using the linear up/log down trapezoidal rule
AUMCextr	Extrapolated Area Under the first Moment Curve from time tlast to infinity, expressed as percentage of AUMCinf	
Cavg	Average drug concentration over a dosing interval	AUCτ/ τ

Parameter Symbol (used in CSP/SAP/ CSR)	**Definition**	**Derivation**
C0	Drug concentration in plasma at time zero following bolus intravenous injection	
Clast	Last observed (quantifiable) concentration	
Cmax	Maximum observed plasma (peak) drug concentration	
Cmin	Minimum observed plasma drug concentration	
Ctrough	Observed lowest drug concentration reached before the next dose is administered	
CL	Total body clearance of drug from plasma after intravascular administration	$Dose_{IV}$/AUCinf
CL/F	Apparent total body clearance of drug from plasma after extravascular administration	Dose/AUCinf
λz	Terminal elimination rate constant	Estimated from linear regression of the terminal part of the log concentration versus time curve
λz lower	Lower (earlier) t used for λz determination	
λz upper	Upper (later) t used for λz determination	
λzN	Number of data points used for λz determination	
λz span ratio	Time period over which λz was determined as ratio of t½λz	λz period (i.e., λz upper- λz lower) /t½λz
F	Fraction of administered dose systemically available / absolute bioavailability	(AUCinf/$AUCinf_{IV}$) x ($Dose_{IV}$/Dose)
Frel	Fraction of administered dose systemically available relative to standard reference such as alternative formulation (note: not iv) / relative bioavailability	(AUCinf/$AUCinf_{REF}$) x ($Dose_{REF}$/Dose)

Parameter Symbol (used in CSP/SAP/ CSR)	**Definition**	**Derivation**
MRTinf	Mean residence time of the unchanged drug in the systemic circulation	AUMC/AUCinf
Rac AUC, Cmax	Accumulation ratio for AUC, Cmax	Steady state AUCτ/first dose AUCτ, Steady state Cmax/first dose Cmax
Rsq	Statistical measure of fit for the regression used for λz determination	
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)	
tmax	Time to reach peak or maximum observed concentration or response following drug administration	
tmin	Time of occurrence of Cmin	
tlag	Time delay between drug administration and the first observed concentration in plasma	
tlast	Time of last observed (quantifiable) concentration	
TCP	Temporal change parameter in systemic exposure (also known as: time dependency, temporal parameter change, linearity index)	Steady state AUCτ /first dose AUCinf Steady state Cmax/first dose Cmax
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve	ln 2/λz
Vss	Volume of distribution at steady state from an iv dose	MRT x CL
Vss/F	Volume of distribution (apparent) at steady state following extravascular administration	MRT x CL/F
Vz	Volume of distribution following iv administration (based on terminal phase)	CL/λz

Parameter Symbol (used in CSP/SAP/ CSR)	Definition	Derivation
Vz/F	Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase)	(CL/F)/λz

Points to consider for selection of data points for estimating the elimination rate constant

The terminal elimination rate constant (lambda z [λz]) is calculated by log-linear regression of the terminal portion of the concentration time profile. The following points should be considered and, and in general, should ensure a good estimate of λz:

- If there is more than one phase apparent, use only data points from the terminal phase.
- Use 3-6 measured concentrations spanning three half-lives.
- Include the last measurable concentration if possible.
- Include only observations after Cmax.
- The Rsq value shows the goodness-of-fit (the precision) in the choice of points. The Rsq adjusted value also shows the goodness-of-fit but takes into consideration the number of points used in the estimation. To achieve a good precision in the estimation, the Rsq adjusted value should be high, e.g., a value of >0.8 is indicative of a good correlation.

Alternative approaches may adequately meet study objectives. In such cases, reported diagnostic parameters should be referred to and precision discussed in the CSR as necessary.

Points to consider for Area Under the Curve zero to infinity

The extrapolated area under the plasma concentration vs. time curve is calculated using the trapezoidal rule. In general, the 'Linear up/Log down' calculation method is appropriate.

To ensure a robust estimate of AUCinf, the extrapolation (AUCextr) should be relatively small as a percentage of the whole AUCinf (e.g., ≤20%).

Alternative approaches may adequately meet study objectives. In such cases, reported diagnostic parameter AUCextr should be referred to and accuracy and precision discussed in the CSR as necessary.

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