A Phase 2a Randomised, Double Blind, Multi-centre Study to Assess the Effect on Glucose Homeostasis of Two Dose Levels of AZD9567, Compared to Prednisolone, in Adults with Type 2 Diabetes

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Protocol Amendment No. 2: Final 3.0, 03 Mar 2021

Clinical Study Protocol	
Study Intervention	AZD9567
Study Code	D6470C00005
Version	3.0
Date	03 March 2021

A Phase 2a Randomised, Double Blind, Multi-centre Study to Assess the Effect on Glucose Homeostasis of Two Dose Levels of AZD9567, Compared to Prednisolone, in Adults with Type 2 Diabetes

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, SE-15185 Södertälje, Sweden

Regulatory Agency Identifier Number(s) EudraCT 2020-000931-35

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

Protocol Number: D6470C00005

Amendment Number: 2

Study Intervention: AZD9567 and prednisolone

Study Phase: 2a

Short Title: Phase 2a, Randomised, Double Blind, Multi-centre Study to Assess the Effect on Glucose Homeostasis of Two Dose Levels of AZD9567, Compared to Prednisolone, in Adults with Type 2 Diabetes

Medical Monitor Name and Contact Information will be provided separately

National co-ordinating Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	03-Mar-2021
Amendment 1	14-Sep-2020
Original Protocol	01-Jul-2020

Amendment 2 (03-Mar-2021)

Overall Rationale for the Amendment:

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis (Number of Participants)	Latest estimated date of last participant completed changed from Feb 2021 to May 2021	Revised to reflect latest estimated date	Non-substantial
Section 1.1 Synopsis (Statistical methods) Section 9.4.1 General Considerations Section 9.4.2.1 Primary Endpoint(s) Section 9.4.2.2 Secondary Endpoint(s) Section 9.4.2.3 Tertiary/Exploratory Endpoints	Mixed model repeated measures analysis changed to linear Following text deleted: Normality assumptions will be tested and if warranted log-transformations will be done prior to performing the analysis Addition of text as follows: and the ratio between them Addition of 'and placebo versus 5 mg prednisolone' to the following text: The treatment comparisons of interest are the different doses of AZD9567 versus the different doses of prednisolone Text regarding exploratory endpoints revised	For clarity	Non-substantial
Section 1.1 Synopsis and 9.5 Interim Analysis	Addition of second interim analysis and corresponding text revision	Progress decision	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3 Schedule of Activities	Timepoint of serum cortisol, CCI and ACTH samples clarified: For the MMTT a standardized mixed meal is to be provided around 07:00 on Day -1 and Day 4 (in each period). Serum cortisol, CCI and ACTH are to be collected from the fasting MMTT blood samples, which is -15 minutes prior to the mixed meal on Days -1 and 4 (in each period)	To address discrepancy	Non-substantial
	Text in footnote m revised for clarity as follows: CGM will be performed during baseline (72h) and treatment period (72h), CGM/FGM will be fitted on Day -4 and removed on Day 4 (in each period) after assessments on Day 3 (in each period) are completed to ensure 2 continuous 72h monitoring periods covering baseline and treatment		
	Revision to clarify that all adverse events will be collected from time of signature of informed consent		
	Text revised to clarify that COVID-19 symptom telephone screening should be done prior to each visit, including Visit 6		
	Text included to clarify that fasting is not required for haematology and clinical chemistry on Day -2 (in each period)	To clarify fasting requirement on Day -2 (in each period)	
	Text revised that COVID-19 phone call will be done one day prior to visit	To clarify timepoint of COVID-19 phone call	
Section 1.3 Schedule of Activities and Section 8.3.4 Clinical Safety Laboratory Assessments (Table 6)	Footnote added to SoA for cortisol, CCI and ACTH to match footnote in Table 6 and included cortisol in footnote c in Table 6	To address discrepancy	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3 Schedule of Activities and Section 9.4.3.1 Adverse Events	Text revised to clarify that adverse events after dosing and up to 21 days will be included in tables and that the adverse events occurring after 21 days will be listed separately Other minor revisions to this section	Consistency in AE follow-up for the 2 study periods	Non-substantial
Section 1.3.1 Blood Sampling Schedule for Mixed Meal Tolerance Tests (MMTTs)	Removed '(minutes)' in body of first column and add to heading of second column and abbreviation for FFAs added to footnote	Administrative change	Non-substantial
Section 1.1 Synopsis (Objectives and Endpoints Table) and Section 3 Objectives and Endpoints	CCI [redacted]	Aligning with the sampling points	Non-substantial
	Definition provided for $\Delta I_{10}/\Delta G_{10}$, $\Delta I_{30}/\Delta G_{30}$, $\Delta C_{10}/\Delta G_{10}$, $\Delta C_{30}/\Delta G_{30}$, HOMA-IR, and HOMA-S		
Section 4.1.1 Order of Assessments	Text revised as follows: Safety ECG and vital signs (systolic and diastolic BP, pulse rate) should be taken pre-dose and approximately 1.5 hours after IMP dosing on Days 1 and 28 and corresponding time on Days 4 and 31	To address discrepancy	Non-substantial
	Text revised to clarify aural body temperature should be taken and timing of ECG assessments		
Section 5.1 Inclusion Criteria	Text for contraception requirement revised	To address discrepancy	Non-substantial
	Clarification that Inclusion Number 2 refers to fasting plasma glucose	To correct error	
Section 5.2 Exclusion Criteria	Text revised to clarify that one rescreening per participant is allowed Addition of following: COVID-19 vaccine (regardless of vaccine delivery platform, eg, vector, lipid nanoparticle) 30 days prior to the date of randomisation (from last vaccination or booster dose)	To clarify rescreening and addition of COVID-19 vaccination criterion	Non-substantial
Section 5.3.1 Meals and Dietary Restrictions	Text revised to clarify that overnight fasting is required prior to each dosing, ie, 12 hours prior and 30 minutes after dosing	To clarify fasting requirement for study intervention dosing	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Fasting requirement added for ACTH	To clarify fasting requirement for ACTH	
Section 6.2 Preparation/ Handling/ Storage/ Accountability of Interventions	Text included to clarify that participants should receive the oral suspension first, followed by the capsules	To clarify order of IMP intake	Non-substantial
Section 6.5 Concomitant Therapy	Following text added: If a patient is being considered for enrolment into the study and also being considered for COVID-19 vaccination, the patient must not be randomised until at least 30 days after the last dose of vaccine or booster.	To clarify COVID-19 vaccination in relation to study randomisation.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Text corrected as follows: FPG > 12 mmol/l (216mg/dL)	To correct conversion error	Non-substantial
	COVID-19 vaccination related discontinuation requirement added	To clarify COVID-19 vaccination related participant discontinuation	
Section 8 Study Assessments and Procedures	Blood volume collected from each participant during the study changed from 500 mL to 600 mL and the following text deleted: including any extra assessments that may be required	For consistency with the blood volume noted in consent form	Non-substantial
Section 8.2.2 Mixed Meal Tolerance Test (MMTT)	Text added to clarify that the solid mixed meal should be consumed as fast as the participant can, within 30 minutes	To clarify requirement for completing mixed meal	Non-substantial
CCI [redacted]	CCI [redacted]	Aligning with the sampling points	Non-substantial
Section 9.1 Statistical Hypotheses	Bullet points added for inclusion of Cohort 2 and Cohort 3	For better clarity	Non-substantial
	Addition of following text: Cohorts 2 and 3 are not powered, thus all significance testing should be considered exploratory		

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 9.2 Sample Size Determination	Text regarding significance testing and presentation of Cohorts 2 and 3 results revised	For better clarity	Non-substantial
Section 9.3 Populations for Analyses	Definition of analysis sets updated	To reflect latest definitions as per the statistical analysis plan	Non-substantial
Section 9.4 Statistical Analyses	The following text deleted: be finalised prior to first participant in and it will	For better clarity	Non-substantial
Section 9.4.2.1 Primary Endpoint(s)	Addition of following: The following comparison will be performed: • 72 mg AZD9567 versus 40 mg prednisolone (Cohort 1). • 40 mg AZD9567 versus 20 mg prednisolone (Cohort 2). • Placebo versus 5 mg prednisolone (Cohort 3). Deletion of following: Normality assumptions will be tested and, if warranted, log transformations will be done prior to performing the analysis. Further details will be provided in the SAP. Text revised from "Should there be more than 10% of participants erroneously treated, a sensitivity analysis will be performed using the actual treatment received." To "Should there be more than 10% of participants erroneously treated, a sensitivity analysis will be performed on the per protocol set."	For better clarity	Non-substantial
Section 9.4.2.2 Secondary Endpoint(s)	Text regarding analysis methods updated	For better clarity	Non-substantial
Appendix F	Addition of COVID-19 related restriction	To clarify COVID-19 vaccination related restriction	Non-substantial
Appendix H Protocol Amendment History	Amendment history for previous version moved to Appendix H	For consistency with latest template	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Global	Minor editorial corrections (typos, formatting, etc)	Document quality	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a Randomised, Double Blind, Multi-centre Study to Assess the Effect on Glucose Homeostasis of Two Dose Levels of AZD9567, Compared to Prednisolone, in Adults with Type 2 Diabetes

Short Title: Phase 2a, Randomised, Double Blind, Multi-centre Study to Assess the Effect on Glucose Homeostasis of Two Dose Levels of AZD9567, Compared to Prednisolone, in Adults with Type 2 Diabetes

Rationale:

AZD9567 is a glucocorticoid receptor (GR) modulator that shows promising separation between anti-inflammatory and dysglycaemic effects in preclinical studies and in two dose escalation studies in healthy volunteers (D6470C00001 and D6470C00002). In addition, in a study in patients with active rheumatoid arthritis (RA) (D6470C00003), 40 mg AZD9567 resulted in a similar profile in term of efficacy effects to prednisolone 20 mg following 14 days of once daily dosing. The aim of this study is to assess the effect on glycaemic control of AZD9567 as compared to prednisolone in a more relevant patient population.

The doses used (40 mg AZD9567 [equipotent to 20 mg prednisolone] and 72 mg AZD9567 [equipotent to 40 mg prednisolone]) were chosen based on studies D6470C00001 and D6470C00002 (equipotency was based on ex-vivo lipopolysaccharide [LPS] stimulated tumour necrosis factor alpha [TNFα] release in whole blood). In study D6470C00002, the effect of several doses of AZD9567 up to 80 mg (equipotent to 45 mg prednisolone) on plasma glucose was investigated and compared with prednisolone. After an oral glucose tolerance test (OGTT) the area under the concentration-time curve from 0 to 4 hours post-dose, AUC(0-4), was measured. The result showed that the effect of AZD9567 80 mg on glucose was similar to the lower dose of 5 mg prednisolone despite being equipotent to 45 mg prednisolone.

This is a randomised, double blind, multi-centre, double dummy, two-way cross-over study to assess the effect on glycaemic control of AZD9567, as measured by the glucose AUC(0-4) versus baseline following a standardised mixed meal tolerance test (MMTT), compared to prednisolone in adults with type 2 diabetes mellitus (T2DM). This study will also evaluate the safety, tolerability, and pharmacokinetics (PK) of AZD9567.

Objectives and Endpoints

Objectives	Endpoints/Outcome Measures
Primary	
• To determine the pharmacodynamic (PD) effect of AZD9567 on glucose homeostasis compared to prednisolone	• **Primary endpoint:** Change in glucose AUC(0-4) versus baseline compared to prednisolone following a standardised mixed meal tolerance test (MMTT)
Secondary	
• To determine the effect of AZD9567 on continuous glucose monitoring (CGM) compared to prednisolone	• Mean daily glucose at 48 - 72 hours treatment as determined from multiple measures via the CGM system • Rise in mean daily glucose over 24-hour periods from start of investigational medicinal product (IMP) dosing (0 - 24 hours, 24 - 48 hours, 48 - 72 hours)
• To determine the PD effect of AZD9567 following a MMTT compared to prednisolone	• Change from baseline in fasting glucose • Change from baseline AUC(0-4) on hormones related to glucose homeostasis (insulin, glucagon, glucagon-like peptide-1 [GLP-1], glucose-dependent insulin releasing polypeptide [GIP]) and free fatty acids (FFAs)
• To determine the PD effect of AZD9567 on glucose homeostasis through an MMTT in comparison to prednisolone	• Change from baseline in AUC(0-4) on insulin and C-peptide
• To determine the PD effect of AZD9567 on derived measures of beta cell function from the MMTT compared to prednisolone	• MMTT derived first phase insulin response ($\Delta I_{10}/\Delta G_{10}$, $\Delta I_{30}/\Delta G_{30}$, $\Delta C_{10}/\Delta G_{10}$, $\Delta C_{30}/\Delta G_{30}$ – where, Δ: change from baseline, I: insulin, C: C-peptide, G: glucose) • Homeostatic model assessment of insulin resistance (HOMA IR),

	homeostatic model assessment of insulin sensitivity (HOMA S)
• To determine the effect of AZD9567 on urinary sodium (U-Na) and urinary potassium (U-K) excretion compared to prednisolone	• 24-hour sodium and potassium concentration
• To evaluate the PK of AZD9567 following once daily dosing	• Plasma PK parameters
• To collect plasma samples for analysis of prednisolone. Reported outside the CSR	• Plasma concentrations of prednisolone
• To explore the relationship between AZD9567 exposure and inhibition of LPS-stimulated TNFα release for high and low dose comparison (Cohort 1 and Cohort 2)	• TNFα concentrations
Safety Objectives	
• To evaluate the safety and tolerability of AZD9567 compared to prednisolone	• Adverse events (AEs)/Serious adverse events (SAEs) • Vital signs • Electrocardiograms (ECGs) • Changes in clinical chemistry/haematology parameters • Morning serum cortisol • Adrenocorticotropic hormone (ACTH)

For Tertiary/Exploratory objectives and outcome measures, see Section 3 of the Clinical Study Protocol (CSP).

Overall Design

This is a randomised, double blind, multi-centre, double dummy, two-way cross-over study with the primary objective of determining the effect of AZD9567 on glucose homeostasis (ie, glycaemic control) versus a dose of prednisolone expected to deliver similar anti-inflammatory effects, as assessed by the change in glucose AUC following the standardised MMTT compared to baseline. Approximately 46 participants with T2DM will be randomised into the study, which will be conducted in Germany.

AZD9567 will be administered once daily as an oral suspension at two dose levels (40 mg/day and 72 mg/day). Prednisolone capsules will be administered orally at three different dose levels (5 mg/day, 20 mg/day, and 40 mg/day). There will be three separate, two-way cross-over cohorts, with three different dose combinations (72 mg AZD9567/40 mg prednisolone, 40 mg AZD9567/20 mg prednisolone, and placebo/5 mg prednisolone). Since the investigational medicinal product (IMP) has different formulations, it will be administered in a double dummy fashion, with each participant taking both oral suspension and capsules of prednisolone/placebo.

Participants who meet all eligibility criteria will be randomised in a ratio of 1:1 to a cohort and sequence group as shown in the Cohorts and Duration section below.

Disclosure Statement: This is a cross-over study with three separate two-way cross-over sequence groups that is participant and investigator blinded.

Number of Participants:

Approximately 46 participants will be randomly assigned to study intervention with a view to achieve 40 evaluable participants completing the study.

Study period		Phase of development
Estimated date of first participant enrolled	Sep 2020	Phase 2a
Estimated date of last participant completed	May 2021	Phase 2a

Cohorts and Duration:

There will be three dose comparisons, each in a separate two-way cross-over:

- **Cohort 1**: participants will be randomised in a ratio of 1:1 to receive AZD9567 and prednisolone over two 72-hour periods in a cross-over design (72 mg AZD9567 followed by 40 mg prednisolone [AB sequence group] or 40 mg prednisolone followed by 72 mg AZD9567 [BA sequence group]). There will be a 3-week washout period between treatment periods. (N=24 completed [12 in each sequence group].)
- **Cohort 2**: participants will be randomised in a ratio of 1:1 to receive AZD9567 and prednisolone over two 72-hour periods in a cross-over design (40 mg AZD9567 followed by 20 mg prednisolone [AB sequence group] or 20 mg prednisolone followed by 40 mg AZD9567 [BA sequence group]). There will be a 3-week washout period between treatment periods. (N=8 completed [4 in each sequence group].)
- **Cohort 3**: participants will be randomised in a ratio of 1:1 to receive placebo and prednisolone over two 72-hour periods in a cross-over design (placebo followed by 5 mg prednisolone [AB sequence group] or 5 mg prednisolone followed by placebo [BA

sequence group]). There will be a 3-week washout period between treatment periods. (N=8 completed [4 in each sequence group].)

Participants will be expected to take part in the study (from screening to follow-up) for 79 days; the study duration may be extended for screening and washout (see Schedule of Assessments [SoA] in Section 1.3).

Statistical methods

For Cohort 1, with a total sample size of 24 participants we can detect an absolute difference of 10% change from baseline in glucose AUC(0-4) (mmol/L 4h), ie, a difference of ~134 mmol/L 4h between prednisolone and AZD9567, with a power of 80% and significance level of 0.05, 1-sided test. Withdrawn participants should be replaced to ensure that 24 participants are evaluable (12 in each sequence group).

The primary PD variable, change from baseline in glucose AUC(0-4) following a standardised MMTT, will be analysed using a linear mixed model with baseline included as covariate. Treatment, period and sequence will be included as fixed effects with participant within sequence as random effect. Models will be run separately for each cohort. Should there be more than 10% of participants erroneously treated, a sensitivity analysis will be performed using the actual treatment received instead. Descriptive statistics and graphical presentations will be presented.

Mean daily glucose measured by continuous glucose monitoring (CGM) is a secondary endpoint and will be analysed using a MMRM analysis with baseline as covariate. Treatment, period and sequence will be included as fixed effects, participant within sequence as random effect and day as repeated measure. Models will be run separately for each cohort. Similar analyses will be performed for the rise in mean daily glucose over 24-hour periods. Fasting glucose as derived from the baseline measure in the MMTT, change in hormones related to glucose homeostasis in response to MMTT (insulin, glucagon, GLP-1, glucose-dependent insulin releasing polypeptide [GIP]), changes in FFAs during MMTT, HOMA-IR, HOMA-S, and 24-hour U-Na and U-K excretion and the ratio between them will be analysed in a similar way to the primary PD endpoint.

Safety will be assessed by descriptive analysis of adverse events (AEs)/serious AEs (SAEs), vital signs, ECGs, clinical laboratory assessments (clinical chemistry/haematology), morning serum cortisol, and adrenocorticotropic hormone (ACTH).

Continuous data will be summarised using descriptive statistics (number of observations, mean, standard deviation, median, 25th and 75th percentiles [where appropriate], minimum and maximum). For log-transformed data it is more appropriate to present geometric mean, geometric coefficient of variation, median, minimum, and maximum. Frequencies and percentages will be used for summarising categorical (discrete) data. Time parameters (tmax,

tlast, etc) will be presented as minimum, median, and maximum only. Confidence intervals and p-values, when presented, will generally be constructed at the 2-sided 95% level. Unless otherwise stated, summaries will be presented by cohort and treatment. The treatment comparisons of interest are the different doses of AZD9567 versus the different doses of prednisolone and placebo versus 5 mg prednisolone. No formal comparisons between the different AZD9567 doses will be conducted. Similarly, no formal comparisons between the different prednisolone doses will be conducted.

The primary analysis population for pharmacodynamics will be the full analysis set. The primary analysis population for safety will be the safety analysis set. The PK analysis set will include all participants who received at least one dose of study intervention and for whom there is at least one reportable PK concentration, no important protocol deviations, or AEs considered to have an effect upon PK.

Two interim analyses are planned to evaluate the feasibility of the assumptions and conduct sample size re-estimation if required (see Section 9.5).

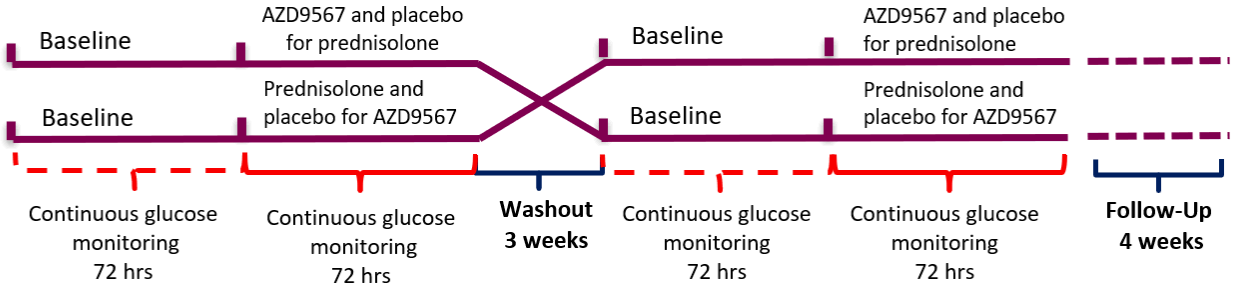
1.2 Schema

Figure 1 Study Flow Diagram

Two-way cross over design repeated for, in total, three comparisons divided into three different cohorts

Participants will be treated for two periods of 72 hours in a cross-over design. There will be a 3-week washout period between treatment periods and a follow-up after 4 weeks

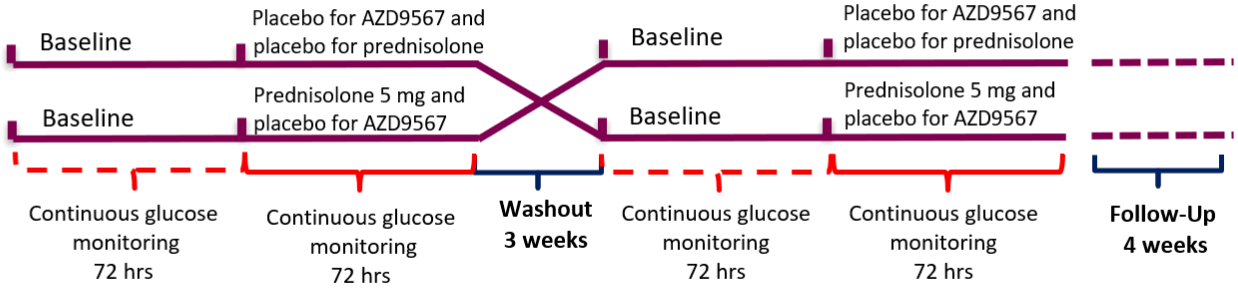
Cohorts 1 and 2:



Cohort 1: 72 mg AZD9567 and 40 mg prednisolone. Twelve participants per arm, in total n = 24 completed

Cohort 2: 40 mg AZD9567 and 20 mg prednisolone. Four participants per arm, in total n = 8 completed

Cohort 3:



Cohort 3: Placebo and 5 mg prednisolone. Four participants per arm, in total n = 8 completed

n: number of participants.

1.3 Schedule of Activities

Visit	1	2	Visit 3 [a]						Washout (3 weeks) [b]	4	Visit 5 [a]						6	Comments
Phase	Screening	Outpatient visit	Residency in Unit [a]							Outpatient visit	Residency in Unit 2 [a]						Final/ET visit [c]	
Timing	≤ 14 days before start of IMP [d]	DAY															Follow-up 30 +/- 4 days after last dose of IMP	
		-4	-2	-1	1	2	3	4		24 (-4)	26 (-2)	27 (-1)	28 (1)	29 (2)	30 (3)	31 (4)		
Informed consent	X																	See Appendix A
Verify eligibility criteria	X			X							X [e]							See Sections 5.1 and 5.2
COVID-19 symptom telephone screening	X [f]	X [f]	X [f]							X [f]	X [f]						X [f]	Phone call to confirm absence of COVID-19 symptoms [f]
COVID-19 PCR test	X		X								X							Further tests at the discretion of the investigator
COVID-19 serology	X										X						X	Further tests at the discretion of the investigator
Demography	X																	
Height and weight	X		X								X						X	Height at screening only Section 8.3.1
Medical History	X																	
Physical examination	X		X [g]					X [g]			X [g]					X [g]	X	Section 8.3.1
Tobacco use	X		X								X							See Section 5.3.2
Alcohol breath test	X		X								X							See Section 8.3.5.1
Safety ECG	X				X [h]			X					X [h]			X	X	Section 8.3.3
Vital signs	X		X		X [h]			X			X		X [h]			X	X	Section 8.3.2

Visit	1	2	Visit 3 [a]						Washout (3 weeks) [b]	4	Visit 5 [a]						6	Comments
Phase	Screening	Outpatient visit	Residency in Unit [a]							Outpatient visit	Residency in Unit 2 [a]						Final/ET visit [c]	
Timing	≤ 14 days before start of IMP [d]	DAY															Follow-up 30 +/- 4 days after last dose of IMP	
		-4	-2	-1	1	2	3	4		24 (-4)	26 (-2)	27 (-1)	28 (1)	29 (2)	30 (3)	31 (4)		
Randomisation in IVRS/IWRS			X															
Adverse events	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Section 8.4
Concomitant medication [i]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	See Section 6.5 and Appendix F
BLOOD SAMPLE COLLECTION																		
Haematology	X		X		X			X			X		X			X	X	Section 8.3.4 Fasting sample not required for Day -2 and Day 26
Clinical chemistry (including trigycerides and HDL-C)	X		X		X			X			X		X			X	X	Section 8.3.4 Fasting sample not required for Day -2 and Day 26
Coagulation (INR, PT and aPTT)	X																	Section 8.3.4
Serology (HIV I and II, HAV, HbsAg and HCV antibody, tuberculosis)	X																	Section 8.3.4
HbA1c	X																	Section 8.3.4
Pregnancy test (hCG)	X																X	Section 8.3.4. Females only

Visit	1	2	Visit 3 [a]						Washout (3 weeks) [b]	4	Visit 5 [a]						6	Comments
Phase	Screening	Outpatient visit	Residency in Unit [a]							Outpatient visit	Residency in Unit 2 [a]						Final/ET visit [c]	
Timing	≤ 14 days before start of IMP [d]	DAY															Follow-up 30 +/- 4 days after last dose of IMP	
		-4	-2	-1	1	2	3	4		24 (-4)	26 (-2)	27 (-1)	28 (1)	29 (2)	30 (3)	31 (4)		
TNFα [j]							X								X			• Pre-dose • Post-dose 1, 2, 4, 8, 12, 24 hours [k] • Section 8.2.4
PK (AZD9567)							X	X							X	X		• Pre-dose • Post-dose 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30 hours [k] • Section 8.6.1
PK (prednisolone)							X	X							X	X		• Pre-dose • Post-dose 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30 hours [k] • Section 8.6.1
Genetic research			X															Section 8.8 and Appendix D

Visit	1	2	Visit 3 [a]					Washout (3 weeks) [b]	4	Visit 5 [a]						6	Comments
Phase	Screening	Outpatient visit	Residency in Unit [a]						Outpatient visit	Residency in Unit 2 [a]						Final/ET visit [c]	
Timing	≤ 14 days before start of IMP [d]	DAY														Follow-up 30 +/- 4 days after last dose of IMP	
		-4	-2	-1	1	2	3	4		24 (-4)	26 (-2)	27 (-1)	28 (1)	29 (2)	30 (3)	31 (4)		
MMTT				X				X				X				X		A standardised mixed meal will be administered around 0700 after an overnight fast. Blood samples to be taken 15 mins pre- and 10, 20, 30, 60, 75, 120, 180, 240 min post-mixed meal intake (see Section 5.3.1) for analysis of plasma glucose, insulin, C-peptide, GLP-1, GIP, glucagon and FFAs, see Sections 1.3.1, and 8.2.2
Serum cortisol				X			X	X				X			X	X	X	Sample to be taken at 0800 [1]
CCI				X			X	X				X			X	X	X	Sample to be taken at 0800 [1]
CCI				X			X	X				X			X	X	X	Sample to be taken at 0800 [1]
ACTH	X			X			X	X				X			X	X	X	Fasted sample to be taken at 0800 [1]

Visit	1	2	Visit 3 [a]						Washout (3 weeks) [b]	4	Visit 5 [a]						6	Comments
Phase	Screening	Outpatient visit	Residency in Unit [a]							Outpatient visit	Residency in Unit 2 [a]						Final/ET visit [c]	
Timing	≤ 14 days before start of IMP [d]	DAY															Follow-up 30 +/- 4 days after last dose of IMP	
		-4	-2	-1	1	2	3	4		24 (-4)	26 (-2)	27 (-1)	28 (1)	29 (2)	30 (3)	31 (4)		
CCI				X			X					X			X			CCI
URINE SAMPLE COLLECTION																		
Urine drug screen (dipstick)	X		X								X							See Section 8.3.5.1
Urinalysis	X		X		X			X			X		X			X	X	Section 8.3.4
U-Na and U-K				X			X					X			X			Sampling over 24 h Section 8.2.3
Pregnancy test (hCG dipstick)					X								X					Section 8.3.4. Females only
STUDY RESIDENCY																		
Admission to CRU			X								X							Admitted to CRU in the early evening on Day -2 (approximately 1700)
Residency at CRU			→								→							
Discharge from CRU								X								X		Discharge around 1800.
CGM/FGM		X [m]	X	X	X	X	X	X		X [m]	X	X	X	X	X	X		CGM/FGM will be fitted on an outpatient basis on Day -4 and removed on Day 4, see Section 8.2.1

Visit	1	2	Visit 3 [a]						Washout (3 weeks) [b]	4	Visit 5 [a]						6	Comments
Phase	Screening	Outpatient visit	Residency in Unit [a]							Outpatient visit	Residency in Unit 2 [a]						Final/ET visit [c]	
Timing	≤ 14 days before start of IMP [d]	DAY															Follow-up 30 +/- 4 days after last dose of IMP	
		-4	-2	-1	1	2	3	4		24 (-4)	26 (-2)	27 (-1)	28 (1)	29 (2)	30 (3)	31 (4)		
Standardised dinner			X				X				X				X			A standardised meal will be given at approximately 1900
IMP ADMINISTRATION																		
IMP dosing at clinic					X	X	X						X	X	X			Dosing will be around 07:00 (± 30 min) See Section 6

[a] Treatment period 1: Day -4 to Day 4. Treatment period 2: Day 24 to Day 31.
[b] Washout period may be extended to 4 weeks to allow for resolution of acute illness or infection. Further extension needs to be discussed with the investigator.
[c] Participants who discontinue IMP early (early termination) will have the same assessments as at the Final/ET visit.
[d] Screening may be extended up to a maximum of 28 days to allow for re-tests or washout of SGLT2i/DDP4i to be completed.
[e] Eligibility criteria to be re-checked before entry to CRU for treatment period 2 (see Section 5.1 and 5.2).
[f] CRU will call participant a day prior to visit to CRU. Participants should also call the site at any time if they think they may be experiencing COVID-19 symptoms.
[g] Brief physical examination.
[h] Pre-dose and 1.5 hours post IMP.
[i] Participants on dual therapy will require 2 weeks washout of SGLT2i or DPP4i.
[j] TNFα will be measured for high and low dose comparison only (Cohort 1 and Cohort 2).
[k] PK post-dose timepoints are over two days (ie, reflect one timepoint series).
[l] Collected from the fasting MMTT blood samples (-15 min) when MMTT is assessed at the same visit.
[m] CGM will be performed during baseline (72 hours) and treatment period (72 hours). CGM/FGM will be fitted on Day -4 and removed on Day 4 (in each period) after assessments on Day 3 (in each period) are completed to ensure 2 continuous 72 hours monitoring periods covering baseline and treatment.

Note: Interim telephone visits may occur at any time during the outpatient periods, as determined by the investigator, to review the safety and well-being of the participant.

Abbreviations: ACTH: adrenocorticotropic hormone; aPTT: activated partial thrombin time; CGM: continuous glucose monitoring; CRU: clinical research unit; DPP4i: Dipeptidyl peptidase-4 inhibitor; ECG: electrocardiogram; ET: end of treatment; FFA: free fatty acid; FGM: flash glucose monitoring; GIP: glucose-dependent insulin releasing polypeptide; GLP-1: glucagon-like peptide-1; HAV: Hepatitis A virus; HbA1c: haemoglobin 1Ac; HbsAg: Hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: Hepatitis C virus; HDL-C: high-density lipoprotein-cholesterol; HIV: human immunodeficiency virus; IMP: investigational medicinal product; INR: International normalized ratio; IVRS/IWRS: Interactive Voice/Web Response System; MMTT: mixed meal tolerance test; PCR: polymerase chain reaction; PK: pharmacokinetics; PT: prothrombin time; SGLT2i: sodium-glucose co-transporter-2 inhibitor; T2DM: type 2 diabetes mellitus; TNFα: tumour necrosis factor alpha; U-K: urinary potassium; U-Na: urinary sodium.

1.3.1 Blood Sampling Schedule for Mixed Meal Tolerance Tests (MMTTs)

	Day -1, Day 4, Day 27, and Day 31 (minutes)	Comments
Plasma glucose, insulin, C-peptide GLP-1, GIP, glucagon, and FFAs	-15, 10, 20, 30, 60, 75, 120, 180, 240	Time point in relation to the start of the meal

Abbreviations: FFA: free fatty acid; GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulin releasing polypeptide

2 INTRODUCTION

2.1 Study Rationale

AZD9567 is a glucocorticoid receptor (GR) modulator that shows promising separation between anti-inflammatory and dysglycaemic effects in preclinical studies and in two dose escalation studies in healthy volunteers (D6470C00001 and D6470C00002). In addition, in a study in patients with active RA (D6470C00003), 40 mg AZD9567 resulted in a similar profile in term of efficacy effects to prednisolone 20 mg following 14 days of once daily dosing. The aim of this study is to assess the effect on glycaemic control of AZD9567 as compared to prednisolone in a more relevant patient population.

The doses used (40 mg AZD9567 [equipotent to 20 mg prednisolone] and 72 mg AZD9567 [equipotent to 40 mg prednisolone]) were chosen based on studies D6470C00001 and D6470C00002 (equipotency was based on ex-vivo lipopolysaccharide [LPS] stimulated tumour necrosis factor alpha [TNFα] release in whole blood). In study D6470C00002, the effect of several doses of AZD9567 up to 80 mg (equipotent to 45 mg prednisolone) on plasma glucose was investigated and compared with prednisolone. After an OGTT the AUC(0-4) was measured. The result showed that the effect of AZD9567 80 mg on glucose was similar to the lower dose of 5 mg prednisolone despite being equipotent to 45 mg prednisolone.

2.2 Background

For more than 60 years, glucocorticoids (GC) have been among the most commonly prescribed drugs, used in treatment protocols of a wide variety of inflammatory and autoimmune diseases. Prednisolone, for example, is used to treat more than 55 indications spanning across several therapeutic areas including but not limited to rheumatology, endocrinology, dermatology, ophthalmology, respiratory, haematology, and gastroenterology. The therapeutic success of GCs originates from their ability to modulate the expression of a wide range of pro-inflammatory mediators. While GCs remain central to anti-inflammatory protocols, it is clear that their prolonged administration influences a diverse set of key biological functions and causes concerning side effects such as developing or worsening of type 2 diabetes mellitus (T2DM), bone loss, increasing risk of infections, cataracts, oedema, weight gain, etc. Glucocorticoids are known to result in whole-body insulin resistance and obesity. Such unwanted effects are the reason that most GCs standard regimens are often short and tapered for the treatment of chronic inflammations. A new agent with a wider therapeutic margin would be expected to be dosed at higher levels for a longer period of time, thus leading to improved efficacy with fewer adverse events (AEs).

AZD9567 is an oral, non-steroidal selective glucocorticoid receptor modulator (SGRM), with potential use as an oral anti-inflammatory treatment for diseases in which GCs are indicated. It is differentiated through a unique binding mode that selectively confers anti-inflammatory

properties similar to traditional GCs but produces a genetic response different to that of prednisolone. Preclinical studies have shown significant anti-inflammatory effect with a differentiation between desired efficacy and the unwanted effects (eg, glucose metabolism, bone effects and mineralocorticoid effect) in nonclinical models and systems. AZD9567 is safe and well tolerated thus far in clinical studies of healthy volunteers and in patients with RA. Therefore, further development of AZD9567 to treat acute or chronic inflammatory condition with minimum steroid AEs such as hyperglycaemia warrants the investigation of oral SGRM compared to prednisolone in patients with T2DM.

To support further development of AZD9567 for inflammatory diseases in subjects with T2DM, this randomised, double blind, two-way cross-over study will assess the effect on glycaemic control of AZD9567 as compared to prednisolone in male and female adults with T2DM, as measured by the change in glucose AUC(0-4) versus baseline following a standardised mixed meal tolerance test (MMTT). This study will also evaluate the safety, tolerability and PK of AZD9567.A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD9567 is provided in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

There is limited experience from human clinical exposure of AZD9567. The following observations are considered relevant based on clinical experience from the use of GCs.

Table 1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
Glucose homeostasis	Glucocorticoid class effects: It is well known that GCs stimulate gluconeogenesis and inhibit the glucose uptake in muscle and adipose tissue. Increased glucose levels and tissue insulin resistance is observed early after exposure with GCs.	Glucose insulin and C-peptide will be measured to evaluate the effects on glucose homeostasis.
Hypothalamus, pituitary gland, and adrenal glands (HPA)-axis	Reduction in plasma cortisol is a physiological and expected response to administration of an exogenous GR agonist. Clinically relevant adrenal insufficiency after a 3-day course of GR agonist treatment is not expected.	Serum cortisol and ACTH will be measured to evaluate effects of AZD9567 on cortisol levels.
Effect on mineralocorticoid axis	Prednisolone has a known effect on the mineralocorticoid axis so it may be	Morning plasma CCI [redacted] to evaluate salt

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	expected that AZD9567 could have an impact	and water retention, will be measured.
Drug-drug interactions	AZD9567 showed a moderate inhibitory potential on drug transporters in in vitro assays and there is a low to moderate risk for drug-drug interactions.	Drugs with transporter mediated absorption such as digoxin should be excluded. Where statins are used, AZD9567 is taken in the morning and the statin in the evening.
Gastrointestinal (GI) effects	Bleeding of the stomach or intestines is an infrequent side effect of long-term treatment of prednisolone. Animal studies have shown that GCs impair both gastric mucus production and gastric bicarbonate secretion which results in weakening of gastric mucosal defences.	Participants with history of previous gastric/duodenal ulcers or surgery affecting the upper GI tract are excluded. Monitoring for GI bleeding will be performed by symptomology, and laboratory testing (haemoglobin measurement).
Fluid and electrolyte disturbances; sodium retention	Long-term administration of GCs can cause fluid and electrolyte disturbances and sodium retention.	Electrolyte balance will be monitored through routine safety laboratory tests.
COVID-19	Participants with T2DM are at risk of complications associated with COVID-19 infection. The effect of short-term treatment with corticosteroids or AZD0567 is unknown on outcomes of COVID-19	There is a very short dosing window for participants in the study, and risk of exposure to COVID-19 will be further reduced by screening participants by phone call before admission for evidence of infection, and advising them to socially isolate where possible. Polymerase chain reaction analysis for COVID-19 has been added at enrolment and upon admission. Negative test is required prior to dosing.
Study Procedures		
None		
Other		
None		

2.3.2 Benefit Assessment

Providing the measures described in Table 1 are followed, it is concluded that the potential benefits compared to risks of evaluating AZD9567 justify its further evaluation in participants

with diabetes.

2.3.3 Overall Benefit: Risk Conclusion

AZD9567 is an oral, non-steroidal, potent SGRM under development for the treatment of patients requiring oral corticosteroid therapy for acute and chronic inflammatory condition in patients at risk of diabetes (or with pre-existing diabetes).

Experience has been gathered from nonclinical safety pharmacology, toxicology studies, previous clinical experience with GR agonists and data from the first in man single ascending dose study (D6470C00001), the MAD study (D6470C00002) and a Phase 2 study in RA patients (D6470C00003, SEMRA). In preclinical testing, AZD9567 displayed features consistent with a potent GR agonist and expected findings in humans will be monitorable and reversible.

In clinical studies of AZD9567, single doses of AZD9567 up to 155 mg, and multiple doses of AZD9567 up to 125 mg have been well tolerated in healthy volunteers. The result of the MAD study (D6470C0002), also showed a good differentiation in plasma glucose compared to prednisolone at doses with similar anti-inflammatory activity. Study D6470C00003, in patients with RA, showed a similar safety profile, good tolerability and similar profile in terms of efficacy. Based on this experience, it is expected that AZD9567 will be well tolerated in participants with diabetes.

In the planned study, participants with T2DM are at risk of complications associated with COVID-19 infection and the effect of short-term treatment with corticosteroids or AZD0567 is unknown on outcomes of COVID-19.

Participants will be contacted by phone before admission to the CRU for evidence of infection and will be advised to socially isolate where possible. Individuals that cannot be enrolled in the study due to ongoing infections may be rescreened if the infections resolve within 4 to 6 weeks. Clinical checks and polymerase chain reaction (PCR) for COVID-19 at screening (see Exclusion Criterion 7) ensures they are free of virus at entry to the study. A telephone call from the site prior to each visit for enrolled patients, plus screening for evidence of infection, have been added to the assessments to minimise the risk of spreading infection. Therefore, with current measures the benefit risk balance is very likely to be similar to that expected before the COVID-19 pandemic.

More detailed information about the known and expected benefits and potential risks of AZD9567 may be found in the IB.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints/Outcome measures
Primary	
To determine the PD effect of AZD9567 on glucose homeostasis compared to prednisolone	• Primary endpoint: Change in glucose AUC(0-4) versus baseline compared to prednisolone following a standardised MMTT
Secondary	
To determine the effect of AZD9567 on CGM compared to prednisolone	• Mean daily glucose at 48 – 72 hours treatment as determined from multiple measures via the CGM system • Rise in mean daily glucose over 24-hour periods from start of IMP dosing (0 – 24 hours, 24 – 48 hours, 48 – 72 hours)
To determine the PD effect of AZD9567 following a MMTT compared to prednisolone	• Change from baseline in fasting glucose • Change from baseline AUC(0-4) on hormones related to glucose homeostasis (insulin, glucagon, GLP-1, GIP) and FFAs
To determine the PD effect of AZD9567 on glucose homeostasis through an MMTT in comparison to prednisolone	• Change from baseline in AUC(0-4) on insulin and C-peptide
To determine the PD effect of AZD9567 on derived measures of beta cell function from the MMTT compared to prednisolone	• MMTT derived first phase insulin response ($\Delta I_{10}/\Delta G_{10}$, $\Delta I_{30}/\Delta G_{30}$, $\Delta C_{10}/\Delta G_{10}$, $\Delta C_{30}/\Delta G_{30}$ - – where, Δ: change from baseline, I: insulin, C: C-peptide, G: glucose) • Homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of insulin sensitivity (HOMA-S)
To determine the effect of AZD9567 on U-Na and U-K excretion compared to prednisolone	• 24-hour sodium and potassium concentration
To evaluate the PK of AZD9567 following once daily dosing	• Plasma PK parameters

Objectives	Endpoints/Outcome measures
To collect plasma samples for analysis of prednisolone. Reported outside the CSR	• Plasma concentrations of prednisolone
To explore the relationship between AZD9567 exposure and inhibition of LPS-stimulated TNFα release for high and low dose comparison (Cohort 1 and Cohort 2)	• TNFα concentrations
Safety	
To evaluate the safety and tolerability of AZD9567 compared to prednisolone	• AEs/SAEs • Vital signs • ECGs • Changes in clinical chemistry/haematology parameters • Morning serum cortisol • ACTH
Exploratory	
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a randomised, double blind, multi-centre, double dummy, two-way cross-over study with the primary objective of determining the effect of AZD9567 on glucose homeostasis (ie, glycaemic control) versus a dose of prednisolone expected to deliver similar anti-inflammatory effects, as assessed by the change in glucose AUC following the standardised MMTT compared to baseline. Approximately 46 participants with T2DM will be randomised into the study, with a view to achieve 40 evaluable participants completing the study. The study will be conducted in Germany.

AZD9567 will be administered once daily as an oral suspension at two dose levels (40 mg/day and 72 mg/day). Prednisolone capsules will be administered orally at three different dose levels (5 mg/day, 20 mg/day, and 40 mg/day). Since the IMP has different formulations, it will be administered in a double dummy fashion, with each participant taking both oral suspension and capsules of prednisolone/placebo.

Each cohort will be treated for two 72-hour periods in a cross-over design, with a 3-week washout period between treatment periods. The total length of participant engagement (from screening to follow-up) is 79 days; the study duration may be extended for screening and washout (see SoA in Section 1.3).

Participants with T2DM who meet all eligibility criteria will be randomised in a ratio of 1:1 to a cohort and sequence group as shown below.

There will be three separate, two-way cross-over cohorts, with three different dose combinations (72 mg AZD9567/40 mg prednisolone, 40 mg AZD9567/20 mg prednisolone and placebo/5 mg prednisolone); see Figure 1:

- **Cohort 1**: participants will be randomised in a ratio of 1:1 to receive AZD9567 and prednisolone over two 72-hour periods in a cross-over design (72 mg AZD9567 followed by 40 mg prednisolone [AB sequence group] or 40 mg prednisolone followed by 72 mg AZD9567 [BA sequence group]). There will be a 3-week washout period between treatment periods. (N = 24 completed [12 in each sequence group].)
- **Cohort 2**: participants will be randomised in a ratio of 1:1 to receive AZD9567 and prednisolone over two 72-hour periods in a cross-over design (40 mg AZD9567 followed by 20 mg prednisolone [AB sequence group] or 20 mg prednisolone followed by 40 mg AZD9567 [BA sequence group]). There will be a 3-week washout period between treatment periods. (N = 8 completed [4 in each sequence group].)
- **Cohort 3:** participants will be randomised in a ratio of 1:1 to receive placebo and prednisolone over two 72-hour periods in a cross-over design (placebo followed by 5 mg

prednisolone [AB sequence group] or 5 mg prednisolone followed by placebo [BA sequence group]). There will be a 3-week washout period between treatment periods. (N = 8 completed [4 in each sequence group].)

In treatment period 1, participants will be fitted with a CGM/Flash Glucose Monitoring (FGM) device on Day -4 on an outpatient basis. Participants will then be admitted to the CRU on Day -2. On Day -1, they will have a baseline MMTT. Dosing of IMP will occur on Days 1 to 3. The CGM/FGM device will be removed on Day 4. Participants will have an MMTT in the morning of Day 4, before being discharged from the CRU in the afternoon of Day 4. This sequence of events will be repeated in the second period (Day 24 to Day 31) (see Section 1.3).

4.1.1 Order of Assessments

It is important that PK and PD sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

1 Safety ECG
2 Vital signs (systolic and diastolic BP, pulse rate, and aural body temperature)
3 Pharmacokinetic blood sampling (will be drawn at the specified time point)
4 Pharmacodynamic blood sampling (will be drawn at the specified time point)
5 Safety blood sampling
6 Urine collections for safety assessments

Safety ECG and vital signs (systolic and diastolic BP, pulse rate) should be taken pre-dose and approximately 1.5 hours after IMP dosing on Days 1 and 28 and corresponding time on Days 4 and 31.

4.2 Scientific Rationale for Study Design and Population

This is a Phase 2a, two-way, cross-over study designed to assess the PD, PK, and safety of AZD9567 in male and female adults with T2DM. The study aims to compare the effects of two different doses of AZD9567 (40 mg/day and 72 mg/day) on glucose homeostasis with prednisolone (5 mg/day, 20 mg/day, and 40 mg/day) and placebo.

Oral GCs are commonly prescribed to treat various inflammatory and autoimmune disorders, including RA. However, GC treatment is associated with several metabolic effects, such as insulin resistance and hyperglycaemia. Patients with type 1 diabetes mellitus and T2DM, or with increased insulin resistance, require a closer monitoring of their glucose levels while on systemic steroids and frequently need increase or modification of their diabetic treatments (Spanakis et al 2014). Therefore, the availability of a GR agonist with less, or devoid of, steroid-related unwanted metabolic effects would provide a valuable health benefit to these patients. From preclinical studies, AZD9567 at equipotent anti-inflammatory doses to

prednisolone is expected to have less effect on the glucose metabolism. Further, the MAD study (D6470C00002) indicated that subjects who were on AZD9567 kept their glycemic control better than subjects on prednisolone.

In order to assess the effect on glucose homeostasis, the populations selected for this study will be male and female adults aged 18 – 75 years with T2DM diagnosis of ≥ 6 months, on stable metformin for ≥ 4 weeks and an HbA1c 6% – 9.5%. These participants, unlike healthy volunteers with normal weights and medical history, show an increased glycemic response to oral steroids (Yuen et al 2012). The population chosen for this study, therefore, will be the most appropriate to assess the effect of AZD9567 on glycemic levels and to compare it to that of prednisolone. The cross-over design of the study is designed to maximise data available on the clinical effect of AZD9567 versus prednisolone, while limiting the number of patients exposed to prednisolone during the study.

4.3 Justification for Dose

The most common prednisolone dosage to treat chronic inflammation is 5 – 60 mg/day, tapered to the minimally effective dose in order to impact disease activity while avoiding systemic adverse effects, including loss of glycemic control (British National Formulary (BNF)).

In this study, prednisolone doses of 5 mg, 20 mg, and 40 mg are selected as low to moderate clinically relevant doses spanning the range of therapeutic doses to relatively situate AZD9567 in terms of effects on glycemic control.

For meaningful assessment of differentiation, it is necessary to compare AZD9567 and prednisolone at doses with equal anti-inflammatory effect. In two recent dose escalation studies in healthy volunteers (D6470C00001 and D6470C00002), AZD9567 and prednisolone were evaluated with respect to anti-inflammatory biomarker effect, using inhibition of the cytokine TNFα from the immune cells, over 24 hours, following LPS stimulation in whole blood.

TNFα was inhibited by both AZD9567 and prednisolone in an exposure-dependent manner. A PK-PD modelling approach was used to establish dose–exposure–response relationships of TNFα for both compounds. Using these relationships, the dose AZD9567 that would produce the same level of TNFα inhibition as a given dose of prednisolone was predicted. A comparison of the dose-response curves enabled estimation of an equipotency relationship. Specifically, 20 mg prednisolone was estimated to be equipotent to 40 mg AZD9567 (95% CI: 29 – 54 mg), and 40 mg prednisolone was predicted to be equipotent to 72 mg AZD9567 (95% CI: 52 – 99) (Almquist et al 2020).

The validity of the equipotency analysis is supported by study D6470C00003 in patients with active RA despite stable treatment with conventional disease-modifying anti-rheumatic drugs,

where 40 mg AZD9567 resulted in a similar profile in term of efficacy effects to prednisolone 20 mg following 14 days of once daily dosing.

When comparing the effect of AZD9567 and prednisolone on glycemic control in healthy volunteers, it was evident that the effect of AZD9567 at doses up to 80 mg on plasma glucose AUC(0–4h) after an OGTT were similar to those observed with 5 mg prednisolone.

Thus, for the assessment of safety differentiation versus prednisolone related to glycemic control in relevant populations such as patients with T2DM, 40 mg AZD9567 (equipotent to 20 mg prednisolone) and 72 mg AZD9567 (equipotent to 40 mg prednisolone) was chosen. The highest dose comparison provides enough power to detect a significant difference in glucose control between treatments, while lower doses will be evaluated on an exploratory basis. This minimises the number of participants and duration of steroid exposure.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed both periods of the study including the last safety follow-up visit (Visit 6) shown in the SoA.

For a participant, the end of study is defined as the date reported in the 'End of Study' electronic Case Report Form (eCRF) for that participant. For all participants, the end of study is defined as the last date reported in the 'End of Study' eCRF for all participants.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Age

1 Participant must be aged 18 to 75 years of age inclusive, at the time of Visit 1.

Type of Participant and Disease Characteristics

2 Participants with diagnosis of T2DM for 6 months prior to screening: HbA1c in the diabetes range or fasting plasma glucose 126 -220 mg/dL.

3 On stable metformin therapy for at least 4 weeks, where no significant dose change (increase or decrease ≥ 500 mg/day) has occurred prior to screening and HbA1c 6% – 9.5%, or on dual therapy with metformin in combination with SGLT2i or DPP4i and HbA1c 6% – 8%. Participants on dual therapy will require 2 weeks washout of SGLT2i or DPP4i.

4 Venous access suitable for multiple cannulations.

Sex

5 Males and females.

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Male participants: All male participants must be willing to avoid fathering a child by either true abstinence[1] or use (together with their female partner/spouse) a highly effective contraception form of birth control in combination with a barrier method, starting from the time of study intervention administration until 3 months after the Final/ET visit. Acceptable methods of preventing pregnancy are provided below.

Reproduction

6 Female participants must be not lactating and not of childbearing potential, defined as those who are surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or are postmenopausal (defined as at least 1 year since last menses and having an elevated [> 40 mIU/mL] follicle-stimulating hormone [FSH] laboratory value at screening).

If sexually active, nonsterilized males who have a female partner of childbearing potential must practice two effective contraceptive measures from screening through at least 3 months after the last dose of IMP has been administered. Note: Male condom plus spermicide is only considered an effective contraceptive measure when used together with another method based on following list **(none of the listed methods are intended to be used alone)**. Highly Effective Methods of Contraception include:

(a) Tubal occlusion
(b) Copper T intrauterine device
(c) Levonorgestrel-releasing intrauterine system (eg, Mirena®)
(d) Medroxyprogesterone injections (eg, Depo-Provera®)
(e) Etonogestrel implants (eg, Implanon®, Norplan®)

[1] Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. It is only acceptable if preferred and usual lifestyle of the participant.

(f) Combined pills

(g) Norelgestromin/ethinyl estradiol transdermal system (eg, Ortho Evra®)

(h) Intravaginal device (eg, NuvaRing®)

(i) Desogestrel (Cerazette®).

Informed Consent

7 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this Clinical Study Protocol (CSP).

8 Provision of informed consent prior to any study specific procedures.

9 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative (see Appendix D).

5.2 Exclusion Criteria

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

Medical Conditions

1 History or presence of type 1 diabetes.

2 History of severe hypoglycaemia or hypoglycaemia unawareness within the last 6 months.

3 History or presence of diabetic foot ulcers.

4 Participants with advanced diabetic complications (eg, symptomatic nephropathy, gastroparesis, proliferative retinopathy, significant atherosclerotic disease, congestive, heart failure etc).

5 History of clinically significant lactic acidosis or ketoacidosis following diagnosis with T2DM.

6 History of, or known significant infection or positivity at Visit 1, including hepatitis A, B, or C, human immunodeficiency virus, tuberculosis (ie, positive result for interferon-γ release assay, QuantiFERON® TB-Gold), that may put the participant at risk during participation in the study.

7 History and / or presence of COVID-19:

(a) Participants who have had a severe course of COVID-19 (ie, hospitalisation, extracorporeal membrane oxygenation [ECMO], mechanically ventilated)

(b) Participants with clinical signs and symptoms consistent with COVID-19, eg, fever, dry cough, dyspnoea, sore throat, fatigue, or confirmed current infection by

appropriate laboratory test within the last 4 weeks prior to screening or on admission to the CRU

(c) Participants with confirmed COVID-19 infection by PCR test before randomisation

8 Donation of blood (≥ 450 mL) within 3 months or donation of plasma within 14 days before Visit 1.

9 History of or current alcohol or drug abuse (including marijuana), as judged by the investigator.

10 Previous psychiatric disorders, including but not limited to:

(a) Participants have been committed to an institution by way of official or judicial order

(b) Any active psychiatric illness associated with unstable weight control or which would result in inability to comply with study requirements

(c) History of severe affective disorder including major depressive or maniac-depressive illness

(d) History of previous steroid psychosis

11 Any latent, acute, or chronic infections or at risk of infection, or history of skin abscesses within 90 days prior to the first administration of IMP at the discretion of the investigator.

12 History of adrenal insufficiency.

13 History or current inflammatory disorder.

14 Any other condition that, in the opinion of the investigator, would interfere with evaluations of the IMP or interpretation of participant safety or study results, including, but not limited to:

(a) History of previous gastric/duodenal ulcers or surgery affecting the upper GI tract likely to affect the interpretation of safety and tolerability data

(b) History of cholelithiasis leading to episodes of acute cholecystitis not treated by cholecystectomy, or known biliary disease

(c) History or presence of dyspepsia or oral intolerance to steroids

(d) History of cancer, with the exception of non-melanoma skin cancer which is considered cured based on investigator assessment

(e) History or presence of any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs

15 History of severe allergy/hypersensitivity to AZD9567 or any of the excipients of the product, or ongoing clinically important allergy/hypersensitivity as judged by the investigator.

Prior/Concomitant Therapy

16 Oral or parenteral steroids 8 weeks prior to randomisation and during the study. Topical and inhaled steroids 4 weeks prior to randomisation are acceptable.

17 Use of any prohibited medication during the study or if the required washout time of such medication was not adhered to (see Section 6.5 for details).

18 Receipt of:

- Live or live attenuated vaccine within 4 weeks prior to the first administration of IMP.
- COVID-19 vaccine (regardless of vaccine delivery platform, eg, vector, lipid nanoparticle) 30 days prior to the date of randomisation (from last vaccination or booster dose).

19 Planned in-patient surgery, major dental procedure, or hospitalisation during the study.

Prior/Concurrent Clinical Study Experience

20 Previous participation or participation in any other research study within 1 month prior to Visit 1.

21 Patient treated with any investigational drug within 30 days (or 5 half-lives, whichever is longer) prior to Visit 1.

Diagnostic Assessments

22 Uncontrolled hypertension (BP > 160 mmHg systolic or > 95 mmHg diastolic).

23 Diagnosis of heart failure and current symptoms regardless of definition, ie, HfpEF, HfrEF.

24 Acute coronary syndrome / unstable angina, coronary intervention procedures (percutaneous coronary intervention or coronary artery bypass graft) within the past 6 months.

25 Stroke within the past 3 months.

26 QTcF > 470 ms or family history of long QT-syndrome.

27 AV-block II-III or sinus node dysfunction with significant pause, not treated with pacemaker.

Other Exclusions

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

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

30 Previous randomisation in the present study.

31 Vulnerable persons (eg, persons kept in detention).

5.3 Lifestyle Considerations

1 Participants who are blood donors should not donate blood for the duration of the study and for 3 months following their last dose of AZD9567.

2 Unusual meal habits and special diet requirements or unwillingness to eat the food provided in the study.

3 Abstain from drugs of abuse for the duration of the study.

5.3.1 Meals and Dietary Restrictions

Standardised meals will be provided to all participants while at the CRU. The exact times of the standardised meals relative to dosing of IMP are shown in the SoA (Section 1.3). No additional food or beverages must be consumed while in the clinical unit.

1 Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 72 hours before the start of study intervention until after the final dose in each treatment period.

2 At screening, participants will be required to fast 12 hours prior to blood sampling for adrenocorticotropic hormone (ACTH) collection.

3 During clinic visits, prior to the MMTT, participants will be given a standardised evening meal and then be required to fast overnight for a minimum of 12 hours. No fluids will be allowed apart from water and participants will need to finish the meal.

4 Participants will be given a standardised mixed meal in the morning prior to the MMTT (see Table 3 and Table 4 below).

5 Participants will be required to fast overnight before each IMP dosing, ie, 12 hours prior and 30 minutes after dosing.

Table 3 Mixed Meal Tolerance Test – Solid Meal (Breakfast)

Amount	Ingredients	Calories kcal	Protein g	Fat g	Carbs g	Fibre g
45 g	Wholemeal bread roll (oat, wheat)	100	4.1	1.2	17.7	2.4
50 g	Wheat bread roll	124	4.1	0.4	25.1	1.5
11 g	Butter	82	0.1	9.2	0.1	0.0
29 g	Cheese 30% fat	77	7.8	4.9	0.0	0.0
20 g	Turkey breast	23	4.6	0.4	0.2	0.0
20 g	Strawberry jam	49	0.1	0.1	12.0	0.0
30 g	Curd cheese 20% fat	33	3.7	1.5	0.8	0.0
	Fruit with yoghurt:					
100 g	Plain yoghurt 1.5% fat	61	5.3	1.5	6.5	0.0
50 g	Pear	31	0.2	0.1	6.2	1.6
56 g	Apple	32	0.2	0.3	6.4	1.1

Amount	Ingredients	Calories kcal	Protein g	Fat g	Carbs g	Fibre g
To rinse:						
100 g	Still mineral water	0	0.0	0.0	0.0	0.0
	Total	**612**	**30.2**	**19.6**	**75.0**	**6.6**
Nutrient relation:						
Energy	612 cal					
	2555 kJ					
	Amount	Relation				
Fibre	6.6 g	2%				
Protein	30.2 g	20%				
Fat	19.6 g	29%				
Carbohydrate	75.0 g	49%				

Table 4 Mixed Meal Tolerance Test – Solid Meal (Breakfast) Vegetarian Option

Amount	Ingredients	Calories kcal	Protein g	Fat g	Carbs g	Fibre g
45 g	Wholemeal bread roll (oat, wheat)	100	4.1	1.2	17.7	2.4
50 g	Wheat bread roll	124	4.1	0.4	25.1	1.5
10 g	Butter	74	0.1	8.3	0.1	0.0
30 g	Cheese 30% fat	79	8.1	5.1	0.0	0.0
25 g	Herb curd 20% fat	24	2.5	1.0	1.0	1.0
18 g	Strawberry jam	44	0.1	0.1	10.8	0.0
30 g	Curd cheese 20%	33	3.7	1.5	0.8	0.0
	Fruit with yoghurt:					
120 g	Plain yoghurt 1,5 %	73	6.4	1.8	7.8	0.0
50 g	Pear	31	0.2	0.1	6.2	1.6
50 g	Apple	29	0.2	0.3	5.7	1.0
To rinse:						
100 g	Still mineral water	0	0.0	0.0	0.0	0.0
	Total	**611**	**29.5**	**19.8**	**75.2**	**6.5**
Nutrient relation:						
Energy	611 cal					
	2554 kJ					

Amount	Ingredients	Calories kcal	Protein g	Fat g	Carbs g	Fibre g
	Amount	Relation				
Fibre	6.5 g	2%				
Protein	29.5 g	19%				
Fat	19.8 g	29%				
Carbohydrate	75.2 g	50%				

5.3.2 Caffeine, Alcohol, and Tobacco

1 During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.

2 During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.

3 Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.3.3 Activity

1 Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who have failed to meet one or more of the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) due to ongoing infections that resolve within 4 to 6 weeks may be rescreened. Only one rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening. Such participants should not be rescreened for at least 14 days (and on a case by case basis) following full resolution of the infection.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the CSP.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 5 Investigational Products

	AZD9567	Prednisolone	Placebo	Placebo
Intervention Name	AZD9567 oral suspension	Prednisolone (modified comparator)	Placebo for AZD9567 oral suspension	Placebo for prednisolone
Type	Drug	Drug	Drug	Drug
Dose Formulation	Oral suspension	Capsule	Oral suspension	Capsule
Unit Dose Strength(s)	4 mg/mL	5 mg	-	
Dosage Level(s)	72 mg/day for 3 consecutive days of each treatment period (Cohort 1) 40 mg/day for 3 consecutive days of each treatment period (Cohort 2)	40 mg/day for 3 consecutive days of each treatment period (Cohort 1) 20 mg/day for 3 consecutive days of each treatment period (Cohort 2) 5 mg/day for 3 consecutive days of each treatment period (Cohort 3)	Placebo for 3 consecutive days of each treatment period (Cohort 3)	Placebo for 3 consecutive days of each treatment period (Cohort 3)
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Active comparator	Placebo	Placebo
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labelling	Oral suspension in bulk vials with a study specific label	Oral capsules in bulk bottles with a study specific label	Oral suspension in bulk vials with a study specific label	Oral capsules in bulk bottles with

	AZD9567	Prednisolone	Placebo	Placebo
				a study specific label

(N)IMP: (non)investigational medicinal product

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 All used and unused supply of AZD9567 and placebo will be destroyed by the site at the end of the study. The certificate of delivery and destruction must be signed in accordance with instructions by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

Labels will be prepared in accordance with GMP and local regulatory requirement. The labels will fulfil GMP Annex 13 requirements and will be translated to local language. Details of storage conditions will be provided on the label of the IMP.

The IMP will be manufactured in accordance with GMP and will be supplied by the sponsor as bulk. AstraZeneca will be responsible for the packaging, labelling and final release in accordance with GMP.

AZD9567 will be delivered in clear glass vials while prednisolone will be provided in bulk bottles. Placebo will be provided in matching vials and bottles in a double dummy fashion.

Participants should receive the oral suspension first, followed by the capsules.

Separate handling instructions for the AZD9567 suspension will be provided for the study by the sponsor.

6.3 Measures to Minimise Bias: Randomisation and Blinding

Participants in Cohort 1 who meet all eligibility criteria will be randomised in a ratio of 1:1 to

receive either 72 mg AZD9567 followed by 40 mg prednisolone (AB sequence group) or 40 mg prednisolone followed by 72 mg AZD9567 (BA sequence group) so that 24 participants (12 in each sequence group) complete. For Cohort 2, participants will be randomised in a ratio of 1:1, 40 mg AZD9567 followed by 20 mg prednisolone (AB sequence group) or 20 mg prednisolone followed by 40 mg AZD9567 (BA sequence group) so that eight participants (four in each cohort) complete. For Cohort 3, participants will be randomised in a ratio of 1:1, to placebo followed by 5 mg prednisolone (AB sequence group) or 5 mg prednisolone followed by placebo (BA sequence group) so that eight participants (four in each cohort) complete.

All participants will be centrally assigned to randomised study intervention using an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarised in SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

The IVRS/IWRS will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

The following personnel will have access to the randomisation list:

- The Covance bioanalytical laboratory
- Clinical Supply Study Lead.

With the exception of personnel authorised to access to the randomisation code, the randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual

participant have been made and documented.

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavour to ensure that there are no differences in time taken to dispense following randomisation. Participants randomised to placebo will receive the corresponding dose volume of solution as participants receiving AZD9567 within the same cohort. All dosing will be performed at the study site.

This third party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomisation/dispensing has been done accurately.

6.4 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

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

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest) that the participant is

receiving at the time of enrolment or receives during the study must be recorded along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Preclinical in vitro data indicate that AZD9567 can inhibit drug transporters such as P-glycoprotein and breast cancer receptor protein. Therefore, digoxin should not be given together with the study intervention due to the risk for elevated plasma levels of digoxin. To avoid drug-drug interaction risks for statins (simvastatin, atorvastatin, rosuvastatin and fluvastatin) dose administration should be separated in time such as the AZD9567 is taken in the morning and the statin in the evening.

AZD9567 is metabolised via CYP3A4 and hence moderate and strong inhibitors or inducers of CYP3A should not be administered during this study since that will affect the plasma concentration of AZD9567. Participants should not have taken any of these medications within 3 days of IMP intake or 5 x t1/2, whichever is longer. Guidance is provided in Appendix F. However, the list in Appendix F is not a complete list, ie, it should be treated with caution.

Systemic corticosteroids should not be administered during this study.

If a patient is being considered for enrolment into the study and also being considered for COVID-19 vaccination, the patient must not be randomised until at least 30 days after the last dose of vaccine or booster.

Other medication considered necessary for the participant's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.6 Intervention After the End of the Study

There will be no study intervention provided after the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation)

study intervention. If study intervention is permanently discontinued, the participant will have the same assessments as at the Final visit and will be discharged with follow-up for any ongoing AEs or evaluations that need to be completed. See the SoA in Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed. Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

If a participant tests COVID-positive during the washout period, they may delay entry into the next dosing period while they recover from COVID-19, and may enter the next treatment period if they are symptom free and PCR-negative.

There is limited data on potential interaction between COVID-19 vaccines and IMP. If COVID-19 vaccination is in the best interest of the participant and the participant is vaccinated during the study then the participant should be discontinued from study intervention and followed as part of the safety analysis population. No COVID-19 vaccinations are allowed during the study treatment and within 7 days from treatment completion (last study dose of study treatment).

A participant will cease to receive any further investigational product if any of the following occur in the participant in question:

1 Withdrawal of consent from further treatment with study intervention or lost to follow-up
2 An AE or SAE that, in the opinion of the investigator or the sponsor, requires treatment withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to treatment
3 More than one episode of severe **hypoglycaemia**
4 Persistent symptomatic **hyperglycaemia** with FPG > 12 mmol/l (216 mg/dL)
5 Dose-limiting symptoms with respect to GI tolerability, even after measures are taken to reduce the risk of vomiting, after discussion with the Medical Monitor
6 QTcF > 500 ms
7 Participant noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
8 Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to the sponsor

Participants who have not received study intervention, regardless of the reason, will not be followed.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an ET visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she is still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

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

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

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

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study will be approximately 600 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Enrolment and Screening Procedures

Enrolment and screening assessments are summarised in the SoA (Section 1.3). The 14-day screening period may be extended up to a maximum of 28 days to allow time for re-tests or washout of SGLT2i/DDP4i to be completed. Medical history, COVID-19 PCR, serology and symptoms, full physical examination, serology, urine drugs of abuse (see Table 7), alcohol (breath), safety ECG and laboratory tests, vital signs, FSH (females only), and pregnancy testing (females only) will be assessed for eligibility. Baseline ACTH, height, weight,

demography and use of concomitant medication will also be recorded.

There is a 20-day washout period between treatment periods. Inclusion/exclusion criteria will be checked before each treatment period. In addition, the site staff will call participants 24 hours before each admission to the CRU to check for any COVID-19 symptoms. Participants should also be advised to call the site at any time if they experience any symptoms that could indicate COVID-19.

8.2 Pharmacodynamic Assessments

8.2.1 Continuous Glucose Monitoring (CGM)/Flash Glucose Monitoring (FGM)

CGM/FGM will be fitted on an outpatient basis on Day -4 and removed on Day 4 of treatment period 1 (Day 24 and Day 31, respectively for treatment period 2). Mean daily glucose will be determined from multiple measures using a CGM device at the time points specified in the SoA in Section 1.3.

8.2.2 Mixed Meal Tolerance Test (MMTT)

On Days -1, 4, 27, and 31, a standardised mixed meal (meal should be consumed as fast as the participant can, within 30 minutes) will be administered in the morning, around 0700, after an overnight fast of 12 hours. Blood samples will be taken according to the schedule in Section 1.3.1 for analysis of glucose, insulin, C-peptide, GLP-1, glucose-dependent insulin releasing polypeptide (GIP), glucagon and FFAs.

8.2.3 24-hour Urinary Sodium (U-Na) and Urinary Potassium (U-K)

On Days -1 and 3 and Days 27 and 30, the concentration of sodium and potassium in urine will be measured over 24 hours.

8.2.4 TNFα Concentrations

On Day 3 and Day 30, blood samples will be obtained from Cohort 1 and Cohort 2 for the determination of TNFα according to the schedule in the SoA (Section 1.3). Samples will be collected according to instructions in the Laboratory Manual. The actual date and time of collection of each sample will be recorded. Samples for determination of TNFα concentrations with and without stimulation with LPS, using TrueCulture Lab System will be analysed by a designated laboratory on behalf of AstraZeneca.

CCI [redacted]

CCI [redacted]

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

- A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities), and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Height (screening only) and weight.

Physical examination will be performed at timelines as specified in the SoA (Section 1.3).

8.3.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Section 1.3), after the participant has rested in the supine position for at least 10 minutes.

On Day 1 and Day 28, the following blood pressure and pulse rate variables will be collected before IMP dosing and approximately 1.5 hours after IMP dosing:

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Pulse (bpm)

Blood pressure will be measured in triplicate, with all readings averaged to give the measurement to be recorded in the eCRF.

The following temperature variable will be collected:

- Aural body temperature (ºC)

8.3.3 Electrocardiograms

A 10-second 12-lead safety ECG will be performed at timelines as specified in the SoA (Section 1.3), after 10 minutes' supine rest. On Day 1 and Day 28, the safety ECG will be obtained before IMP dosing and approximately 1.5 hours after IMP dosing. The investigator will judge the overall interpretation as normal or abnormal and this evaluation will be reported in the eCRF. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the investigator. For all abnormalities (regardless of clinical significance) the specific type and nature of the abnormality will be documented in the eCRF. Clinically significant findings should also be documented on the AE page of the eCRF if applicable. The investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment. All ECG readings will be digitally stored as source documents.

8.3.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry (including triglycerides and HDL-C), haematology, coagulation, urinalysis, and additional laboratory variables (HbA1c [screening only], serum cortisol, ACTH, CCI [redacted] hCG, 24-hour U-Na and U-K, and FFAs) will be taken at the visits indicated in the SoA (Section 1.3).

AEs based on examinations and tests should be reported as described in Section 8.4.5.

The following laboratory variables will be measured.

Table 6 Laboratory Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
White blood cell (WBC) total and differential count	Creatinine
Red blood cell (RBC) count	Bilirubin, total and direct
Platelet count	Alkaline phosphatase (ALP)
Haemoglobin (Hb)	Aspartate transaminase (AST)
Haematocrit (HCT)	Alanine transaminase (ALT)
Mean corpuscular volume (MCV)	Gamma glutamyl transpeptidase (GGT)
Mean corpuscular haemoglobin (MCH)	Potassium
Mean corpuscular haemoglobin concentration (MCHC)	Calcium, total
Neutrophils (absolute)	Sodium
Lymphocytes (absolute)	Uric acid
Monocytes (absolute)	Urea
Eosinophils (absolute)	Phosphate
Basophils (absolute)	Bicarbonate
Reticulocytes absolute count	High sensitivity C-reactive protein (hsCRP)
Urinalysis	Triglycerides
Blood	High-density lipoprotein-cholesterol (HDL-C)
Protein	TSH [a]
24-hour sodium and potassium	**Serology**
Glucose	Human immunodeficiency virus (HIV) I and II [a]
Creatinine	Hepatitis A virus (HAV) antibody [a]
Microscopy (if positive for protein or blood)	Hepatitis B surface antigen (HbsAg) [a]
Other	Hepatitis C virus (HCV) antibody [a]
COVID-19 polymerase chain reaction (PCR)	Tuberculosis [a]
HbA1C [a]	COVID-19
Glucose (fasting)	**Pregnancy testing**
Insulin	Human-beta chorionic gonadotrophin (hCG) (blood and urine dipstick)
C-peptide	Follicle-stimulating hormone (FSH) (serum) [a, b]
Serum cortisol[c]	**Coagulation**
Adrenocorticotropic hormone (ACTH) [c]	International normalized ratio (INR)
Free fatty acids (FFAs)	Prothrombin time (PT)
CCI [redacted]	Activated partial thrombin time (aPTT)
CCI [redacted]	

[a] Screening only.
[b] Females only. FSH assessment is for menopausal status.

[c] Collected from the fasting MMTT blood samples (-15 min) when MMTT is assessed at the same visit. For the MMTT a standardized mixed meal is to be provided around 07:00 on Day -1 and Day 4 (in each period). Serum cortisol, CCI and ACTH are to be collected from the fasting MMTT blood samples, which is -15 minutes prior to the mixed meal on Days -1 and 4 (in each period).

NB. In case a participant shows an AST **or** ALT ≥3xULN together with total bilirubin (TBL) ≥2xULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

8.3.5 Other Safety Assessments

8.3.5.1 Additional Screening Variables

Drugs of abuse and alcohol will be measured at screening and before each treatment period as shown in Table 7.

Table 7 Drugs of Abuse and Alcohol

Alcohol	Methamphetamine
Amphetamine	Opiates
Barbiturates	Propoxyphene
Benzodiazepines	Phencyclidine (PCP)
Cocaine	Cannabinoids
Methadone	Tricyclic anti-depressants (TCA)

Drugs of abuse screen will be done via a urine dipstick. Alcohol screen will be done via a breath sample.

8.4 Adverse Events and Serious Adverse Events

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

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

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

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

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events will be collected from time of signature of informed consent form throughout the treatment period, including the follow-up period, to the Final/ET visit (Visit 6).

SAEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP

that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.4.2 Follow-up of Adverse Event and Serious Adverse Event

Any AEs that are unresolved at the participant's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity of the AE:
  - Intensity rating scale:
    1 Mild (awareness of sign or symptom, but easily tolerated)
    2 Moderate (discomfort sufficient to cause interference with normal activities)
    3 Severe (incapacitating, with inability to perform normal activities)
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome.

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

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

- Causality assessment to other medication

8.4.3 Causality Collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.4.4 Adverse Events Based on Signs and Symptoms

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

8.4.5 Adverse Events Based on Examinations and Tests

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

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.4.6 Hy's Law

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

8.4.7 Reporting of Serious Adverse Events

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

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

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

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

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative (or delegate).

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

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

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

8.4.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study drug

8.4.8.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

8.4.8.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and 3 months following the last dose.

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

8.4.9 Medication Error

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.4.7) and within 30 days for all other medication errors.

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

8.5 Overdose

For this study, any dose of IMP greater than the dose intended to be given will be considered an overdose.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, the investigator

or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see section 8.4.7) and within 30 days for all other overdoses.

8.6 Human Biological Samples

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

8.6.1 Pharmacokinetics

Venous blood samples will be collected for measurement of plasma concentrations of AZD9567 and prednisolone as specified in the SoA in Section 1.3.

Plasma samples for evaluation of the PK of prednisolone will be collected in this study; these will be reported outside the CSR.

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

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

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses. Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.6.1.1 Determination of Drug Concentration

Blood samples for determination of drug concentration of AZD9567 and prednisolone will be assayed using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded (ie, at database

lock).

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

8.6.2 Immunogenicity Assessments (Not Applicable)

Immunogenicity will not be evaluated in this study.

8.6.3 Pharmacodynamics

8.6.3.1 Collection of Samples

Blood samples will be collected for measurement of TNFα (Section 8.2.4). Urine samples will be collected for measurement of 24-hour U-Na and U-K (Section 8.2.3).

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

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

8.7 Human Biological Sample Biomarkers

8.7.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to participate in the mandatory research components of the study. Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3).

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

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

8.8 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA and is subject to agreement in the ICF addendum.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.9 Health Economics/Medical Resource Utilisation and Health Economics (Not Applicable)

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

This study aims to demonstrate that AZD9567 improves glucose homeostasis compared to oral prednisolone.

The null hypothesis for the primary analysis is that there is no difference in the change in glucose AUC(0-4) versus baseline in AZD9567 compared to prednisolone following a standardised MMTT. The following comparison will be performed:

- 72 mg AZD9567 versus 40 mg prednisolone in participants with T2DM (Cohort 1)
- 40 mg AZD9567 versus 20 mg prednisolone in participants with T2DM (Cohort 2)
- Placebo versus 5 mg prednisolone in participants with T2DM (Cohort 3)

As this is a Phase 2a study, no adjustments for multiple testing will be performed. Cohorts 2 and 3 are not powered, thus all significance testing should be considered exploratory.

CCI [redacted]

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[redacted]

9.3 Populations for Analyses

The following populations are defined in Table 8.

Table 8 Populations for Analysis

Population/Analysis set	Description
All Enrolled Participants (ENR)	All participants who sign the ICF prior to any study-related procedures.
All Randomised Participants (RND)	All participants in the ENR randomised to one of the two sequence groups within a cohort. The ENR will be analysed according to the planned sequence or treatment.
Full Analysis Set (FAS)	All participants in the RND who received at least one dose of study intervention. The FAS will be analysed according to the planned treatment and will be used as the primary population for reporting pharmacodynamic data and to summarize baseline characteristics. Any important deviations from randomised treatment will be listed and considered when interpreting the pharmacodynamic data.
Safety Analysis Set (SAF)	All participants in the RND who received at least one dose of study intervention. The SAF will be analysed according to actual treatment.
Per Protocol Analysis Set (PP)	All participants in the FAS who did not have an important protocol deviation considered to have an impact on the analysis of the primary endpoint and who completed the study. The PP will be analysed according to the actual treatment received.
PK Analysis Set (PKAS)	All participants in the FAS with at least one quantifiable AZD9567 concentration and no important protocol deviations, or AEs considered to have an effect upon PK. Participants may be excluded from the PK population if they have an AE of vomiting before 2x the median tmax of the group. Participants in the PKAS will be analysed according to the actual treatment. This population will be defined by the Study Team Physician, Pharmacokineticist and Statistician prior to any analysis.

9.4 Statistical Analyses

The SAP will include a more technical and detailed description of the statistical analyses

described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Analyses will be performed by Parexel, except for the derivation of PK parameters, which will be performed by Covance Clinical Pharmacokinetic Alliance.

Continuous data will be summarised using descriptive statistics (number of observations, mean, SD, median, 25th and 75th percentiles [where appropriate], minimum and maximum). For log-transformed data it is more appropriate to present geometric mean, geometric coefficient of variation, median, minimum and maximum. Frequencies and percentages will be used for summarising categorical (discrete) data. Time parameters (tmax, tlast, etc) will be presented as minimum, median, and maximum only.

Confidence intervals and p-values, when presented, will generally be constructed at the 2-sided 95% level.

Unless otherwise stated, summaries will be presented by cohort and treatment. The treatment comparisons of interest are the different doses of AZD9567 versus the different doses of prednisolone and placebo versus 5 mg prednisolone. No formal comparisons between the different AZD9567 doses will be conducted. Similarly, no formal comparisons between the different prednisolone doses will be conducted.

In general, baseline will be defined as the last observation prior to study intervention in each period. The baseline for CGM/FGM will be the mean of all daily results prior to study intervention. Further details will be described in the SAP.

All statistical analyses will be conducted using SAS® version 9.4.

A complete set of raw data listings will be appended to the final CSR. All tables, figures and listings will be presented as PDF documents without any manual editing (ie, they will appear unmodified as programmed by means of the statistical package).

In general, there will be no imputation of missing data for the safety analyses. Additional details on missing data handling conventions will be provided in the SAP.

Deviations from the protocol will be assessed as “important” or “not-important”. Important deviations from the protocol may lead to the exclusion of participants from any of the study analysis sets. Deviations will be defined before database hard lock. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria

- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoint.
- Receiving incorrect study intervention than randomised to.

All protocol deviations will be discussed at a data review meeting prior to database hard lock in order to define the analysis sets for the study. All important protocol deviations will be listed by participant. Further details will be provided in the SAP.

9.4.2 Pharmacodynamic Effects

9.4.2.1 Primary Endpoint(s)

The primary pharmacodynamic variable is the change from baseline in glucose AUC(0-4) following a standardised MMTT.

The change from baseline in glucose AUC(0-4) will be analysed using a linear mixed model with baseline included as covariate. Treatment, period, and sequence will be included as fixed effects, with participant within sequence as random effect. Models will be run separately for each cohort.

The following comparisons will be performed:

- 72 mg AZD9567 versus 40 mg prednisolone (Cohort 1).
- 40 mg AZD9567 versus 20 mg prednisolone (Cohort 2).
- Placebo versus 5 mg prednisolone (Cohort 3).

Should there be more than 10% of participants erroneously treated, a sensitivity analysis will be performed on the PP set.

Descriptive statistics and graphical presentations will be presented.

9.4.2.2 Secondary Endpoint(s)

Mean daily glucose as measured by CGM will be evaluated as a secondary endpoint.

The mean daily glucose will be analysed using an MMRM analysis with baseline as covariate. Treatment, period, and sequence will be included as fixed effects, participant within sequence as random effect, and day as repeated measure. Models will be run separately for each cohort.

Similar analyses will be performed for the rise in mean daily glucose over 24-hour periods.

The secondary endpoints (insulin, glucagon, GLP-1, GIP), changes in FFAs during MMTT, C-peptide, 24-hour U-Na and U-K excretion and the ratio between them, $\Delta I_{10}/\Delta G_{10}$, $\Delta I_{30}/\Delta G_{30}$, $\Delta C_{10}/\Delta G_{10}$, $\Delta C_{30}/\Delta G_{30}$ and C-peptide will be summarised and analysed by means of a linear model or a mixed model for repeated measurements.

LPS-stimulated whole blood TNFα levels will be evaluated as a secondary endpoint for participants in Cohort 1 and Cohort 2 (high and low dose comparison). For TNFα profiles, the AUC will be estimated and the measurements at the sampling points will be summarised. Descriptive statistics will be tabulated both for the AUC and individual measurement points and treatments comparison will be conducted with ANOVA. Models will be run separately for each cohort.

Further details on statistical analyses will be provided in the SAP.

Descriptive statistics and graphical presentations will be presented as appropriate.

9.4.2.3 Tertiary/Exploratory Endpoint(s)

CCI [redacted]

9.4.3 Safety

Safety will be assessed by descriptive analysis of AEs/SAEs, vital signs, ECGs and clinical laboratory assessments.

Serum cortisol and ACTH will be analysed in a similar manner to the TNFα secondary endpoint. Further details on statistical analyses will be provided in the SAP.

9.4.3.1 Adverse Events

The MedDRA will be used to code AEs.

The number of participants experiencing each AE will be summarised by the MedDRA system organ class and preferred term. The number and percentage of participants with AEs in each different category (eg, causally related, severe, etc) will be summarised, and events in each category will be further summarised by MedDRA system organ class and preferred term.

SAEs will be summarised separately if a sufficient number occur.

Any AE occurring before first study intervention will be included in the data listings but will not be included in the summary tables of AEs. AE summary tables will include only AEs occurring after start of study intervention (first dose).

Any AE occurring after last dosing and up to 21 days after discontinuation of study intervention, within each period, will be included in AE summaries. AEs occurring after 21 days will be listed separately, but not included in summaries.

9.4.3.2 Deaths

Details of any deaths will be listed for all participants.

9.4.3.3 Exposure

Details on study intervention administration will be provided in listings.

9.4.3.4 Other Safety Parameters

Physical examination findings, laboratory tests results (blood glucose, haematology, clinical chemistry and urinalysis), ECG findings and vital signs will be summarised using appropriate descriptive statistics, including observed results and changes from baseline as appropriate.

Time course of laboratory test results, vital signs and ECG data may be summarised graphically.

All analyses of safety outcomes will be performed on the SAF.

9.4.4 Pharmacokinetics

Pharmacokinetic analysis for AZD9567 will be performed by Covance Clinical Pharmacokinetic Alliance on behalf of AstraZeneca Research and Development. Pharmacokinetic parameters will be derived using standard non-compartmental methods using WinNonLin version 8.1 or higher (Certara). All descriptive and inferential statistics will be performed using SAS®, version 9.4.

Where possible the following PK parameters will be assessed for.

AUClast	Area under the plasma concentration versus time curve from zero to the last quantifiable concentration
AUC(0-24)	Area under the plasma concentration versus time curve from zero to 24 hours post-dose
AUC(0-6)	Area under the plasma concentration versus time curve from zero to 6 hours post-dose
Cmax	Maximum observed drug concentration
tmax	Time to reach maximum observed drug concentration
t½λz	Terminal elimination half-life
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
Vz/F	Apparent volume of distribution following extravascular administration

Additional PK parameters may be determined where appropriate.

Further details regarding the calculation and descriptive statistics of the PK parameters will be detailed in the SAP.

9.4.5 Other Analyses

Not applicable.

9.5 Interim Analysis

Two interim analyses are planned, conditional on the recruitment rate. A first interim analysis will be conducted when 50% of the participants of Cohort 1 have completed the study. A second interim analysis is planned after completion of Cohort 1.

The purpose of the first interim analyses is to evaluate the feasibility of the assumptions and conduct sample size re-estimation if required. The second interim analysis serves as main statistical analysis for Cohort 1 and facilitates timely readout prior to finalisation of the exploratory cohorts 2 & 3.

Further details regarding the interim analyses will be provided in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the clinical study protocol (CSP) and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The CSP, CSP amendments, ICF, Investigator's Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the CSP will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

Participants who are rescreened are required to sign a new ICF.

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

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Dissemination of Clinical Study Data

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

A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the source data agreement and computerised data check list for electronic source data.

A 8 Study and Site Start and Closure

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

The first act of recruitment is the first site open and will be the study start date.

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 9 Publication Policy

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

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

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

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

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

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

Life-threatening

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

Hospitalisation

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

Important medical event or medical treatment

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

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

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

Intensity rating scale:

mild (awareness of sign or symptom, but easily tolerated)

moderate (discomfort sufficient to cause interference with normal activities)

severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of

intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

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

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

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

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

The causality assessment is performed based on the available data including enough

information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

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

B 4 Medication Error

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

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

Medication error includes situations where an error.

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

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

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

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

- Errors related to or resulting from IVRS/IWRS – including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)

- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for donated biological samples

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

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

The investigator:

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

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

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

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

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

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

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained no longer than 15 years, or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

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

Inclusion criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Healthy Volunteers and paediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of consent for genetic research:

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in section 7.2 of the main Clinical Study Protocol.

Collection of samples for genetic research

- The blood sample for this genetic research will be obtained from the participants at Visit 3, Day -2. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 3, Day -2, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant data protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

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

E 1 Introduction

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

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

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

The investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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

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

E 2 Definitions

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

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

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

E 3 Identification of Potential Hy's Law Cases

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

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

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

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

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

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition

- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the investigator will:

  – Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  – Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used
  – Complete the three Liver eCRF Modules as information becomes available

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

E 5 Review and Assessment of Potential Hy's Law Cases

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

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

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

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine

whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory tests

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HbsAg HBV DNA [a] HCV RNA [a] IgG anti-HCV IgM anti-HEV
	HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [b]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [b] Transferrin saturation

[a] HBV DNA is only tested when IgG anti-HBc is positive ; HCV RNA is only tested when IgG anti-HCV is positive or equivocal.

[b] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 7 References

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

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

Appendix F Guidance for Restricted Medication

Tables below extracted from FDA webpage.

F 1 Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

Table 5. Classification of In Vivo Inducers of CYP Enzymes (1) (7/28/2011)

CYP Enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP3A	Avasimibe,(5) carbamazepine, phenytoin, rifampin, St. John's wort(3)	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,(4) pioglitazone, prednisolone, rufinamide

(1) Please note the following: This is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm[3].

(2) For a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative PK studies in smokers vs. non-smokers.

(3) The effect of St. John's wort varies widely and is preparation-dependent.

(4) Herbal product.

(5) Not a marketed drug.

Classification of Inhibitors

Table 6. Classification of In Vivo Inhibitors of CYP Enzymes (1) (7/28/2011)
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm[2].

CYP Enzymes	Strong Inhibitors(2) ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors(3) ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors(4) ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,(11)	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin,	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine,

CYP Enzymes	**Strong Inhibitors(2) ≥ 5-fold increase in AUC or > 80% decrease in CL**	**Moderate inhibitors(3) ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL**	**Weak inhibitors(4) ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL**
	indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (12) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	fluconazole, fosamprenavir, grapefruit juice,(11) imatinib, verapamil	cyclosporine, fluoxetine, fluvoxamine, ginkgo,(5) goldenseal,(5) isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link
2. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
3. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
4. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.
5. Herbal product.
6. Gemfibrozil also inhibits OATP1B1.
7. Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolised by CYP3A; fluconazole is a moderate CYP3A inhibitor.
8. Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A;
9. Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2.
10. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
11. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).
12. Withdrawn from the United States market because of safety reasons.

13. If a participant is being considered for enrollment into the study and also being considered for COVID-19 vaccination, the participant must not be randomised until at least 30 days after the last dose of vaccine or booster.

F 2 QT Prolonging Drugs Associated with Torsade de Pointes

Guidance regarding QT prolonging drugs associated with Torsade de Pointes can be found in: www.crediblemeds.org.

Appendix G Abbreviations

Abbreviation or special term	Explanation
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC(0-6)	Area under the plasma concentration versus time curve from zero to 6 hours post-dose
AUC(0-24)	Area under the plasma concentration versus time curve from zero to 24 hours post-dose
AUClast	Area under the plasma concentration versus time curve from zero to the last quantifiable concentration
CCI	[redacted]
BP	Blood pressure
CGM	Continuous glucose monitoring
CI	Confidence interval
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
Cmax	Maximum observed drug concentration
CRO	Contract Research Organisation
CRP	C-reactive protein
CRU	Clinical Research Unit
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CYP3A4	Cytochrome P450 3A4
DAS	Disease Activity Score
DNA	Deoxyribonucleic acid
DPP4i	Dipeptidyl peptidase 4 inhibitor
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ET	End of treatment
FDA	U.S. Food and Drug Administration
FFA	Free fatty acid
FGM	Flash glucose monitoring

Abbreviation or special term	Explanation
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GC	Glucocorticoid
GCP	Good Clinical Practice
GI	Gastrointestinal
GIP	Glucose-dependent insulin releasing polypeptide
GLP-1	Glucagon-like peptide-1
glucose AUC(0-4)	Change in glucose area under the concentration-time curve over 4 hours
GMP	Good Manufacturing Practice
GR	Glucocorticoid receptor
HbA1c	Haemoglobin A1c
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HOMA-IR	Homeostatic model assessment-insulin resistance
HOMA-S	Homeostatic model assessment-insulin sensitivity
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed consent form
IMP	Investigational medicinal product
IVRS/IWRS	Interactive Voice/Web Response System
LPS	Lipopolysaccharide
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MMTT	Mixed meal tolerance test
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SGLT2i	Sodium-glucose co-transporter-2 inhibitor
SGRM	Selective glucocorticoid receptor modulator
SoA	Schedule of Activities

Abbreviation or special term	Explanation
T2DM	Type 2 diabetes mellitus
TNFα	Tumour necrosis factor alpha
t½λz	Terminal elimination half-life
tmax	Time to reach maximum observed drug concentration
ULN	Upper limit of normal
U-K	Urinary potassium
U-Na	Urinary sodium
Vz/F	Apparent volume of distribution following extravascular administration

Appendix H Protocol Amendment History

Amendment 1 (14-Sep-2020)

Overall Rationale for the Amendment:

The protocol was amended following a request from the German regulatory authority to clarify the definition of end of study. In addition, corrections were made for the inconsistencies detailed in the protocol clarification letter dated 20 July 2020 and the schema was updated to better exemplify the double dummy study design.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 4.4 End of Study Definition	End of study was defined for individual participants and all participants	Definition for the end of study was requested by the German regulatory authority	Non-substantial
Section 1.2 Schema	Figure 1 updated to include placebos for active study intervention	To clarify the study design by including the placebos required to ensure the double-dummy design	Non-substantial
Section 1.1 and Section 3 Objectives and Endpoints	The endpoint relating to the pharmacodynamic (PD) objective determining the effect of AZD9567 following a mixed meal tolerance text (MMTT) versus prednisolone was corrected as below (revision in **bold**): Change from baseline AUC(0 4) on hormones related to glucose homeostasis (insulin, glucagon, glucagon-like peptide-1 [GLP-1], glucose-dependent insulin releasing polypeptide [GIP]**) and** free fatty acids **(**FFAs**)**	Free fatty acids (FFAs) are not hormones	Non-substantial
Section 1.1 and Section 3 Objectives and Endpoints	The endpoint relating to the PD objective to determine the effect of AZD9567 on glucose homeostasis through an MMTT versus prednisolone was corrected to remove change from	Change in glucose AUC(0 4) versus baseline compared to prednisolone following a standardised MMTT is already included in the primary endpoint.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	baseline in AUC(0-4) on plasma glucose.		
Section 1.3 Schedule of Activities and Section 8.1 Enrolment and Screening Procedures	Text relating to the extension of the screening period up to 28 days was clarified to include the text in bold below [Screening may be extended]…to allow for re-tests or washout of SGLT2i/DDP4i to be completed.	The extension of the screening period is intended for both re-tests and washout of SGLT2i/DDP4i	Non-substantial
Appendix E6 Laboratory Tests	HCV RNA added to Hy's Law kit table and footnote a (HCV RNA is only tested when IgG anti-HCV is positive or equivocal). The footnote was also clarified to state HBV DNA is only tested when IgG anti-HBc is positive only (previously also stated inconclusive).	Hy's Law kit for viral hepatitis includes HCV RNA	Non-substantial
Global	Minor editorial corrections (typos, formatting, etc).	Document quality	Non-substantial

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