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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Parexel International

AstraZeneca

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SPONSOR SIGNATURE PAGE

Approved by: _____ _____

PPD Date

Global Product Statistician
AstraZeneca

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 0.1	Dec 08, 2020	New document
Draft 0.2	Jan 26, 2021	Analysis sets redefined, certain sections updated
Draft 0.3	Feb 14, 2021	Updates based on version 3.0 of the draft Protocol Amendment 2 (dated 10 Feb 2021)
Draft 0.4	March 04, 2021	Updates based on AZ comments
Draft 0.5	March 12, 2021	Updates based on AZ comments
Final 1.0	April 28, 2021	Updated based on PXL and AZ comments
Final 1.0	May 24,2021	Updated based on PXL and AZ comments during interim analysis n 1.
Final 2.0	Aug 16, 2021	Removal of figures that are not require for CSR. Removed requirement that each cohort should be presented as a separate output.
Final 3.0	Oct 28, 2021	Update the Statistical Analysis Plan (SAP) to v3.0 in order to re-insert texts which had been included in SAP v1.0 but erroneously had been deleted in SAP v2.0. Note: This does not mean a change to the planned analysis but the correction of an error.

LIST OF ABBREVIATIONS

Abbreviation	Explanation
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
AUC(0-4)	Area under the curve from zero to 4 hours post-dose
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]
BLQ	Below the lower limit of quantification
BP	Blood pressure
CfB	Change from baseline
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 Organization
CRP	C-reactive protein
CRU	Clinical Research Unit
CSP	Clinical Study Protocol
gCSR	Clinical Study Report
CSRHLD	Standards for reporting clinical data in a Clinical Study Report or Higher Level Document
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DAS	Disease Activity Score
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DPP4i	Dipeptidyl peptidase 4 inhibitor
ECF	Extracellular fluid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture

ENR	All enrolled subjects
ET	End of treatment
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FFA	Free fatty acid
FGM	Flash glucose monitoring
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/Intercellular fluid
IMP	Investigational medicinal product
IPD	Important Protocol Deviation
IVRS/IWRS	Interactive Voice/Web Response System
LMM	Linear mixed model
LPS	Lipopolysaccharide
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MMTT	Mixed meal tolerance test
NC	Not calculable
PD	Pharmacodynamic(s)
PP	Per Protocol Analysis Set
PK	Pharmacokinetic(s)
PKAS	PK Analysis Set

RA	Rheumatoid arthritis
RND	All randomised subjects
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2i	Sodium-glucose co-transporter-2 inhibitor
SGRM	Selective glucocorticoid receptor modulator
SoA	Schedule of Activities
T2DM	Type 2 diabetes mellitus
TBW	Total body water
TLFs	Tables, listings and figures
TNFα	Tumour necrosis factor alpha
t1/2λz	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

1 INTRODUCTION

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 (rheumatoid arthritis) (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 tumor 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 (oral glucose tolerance test), the AUC(0-4) (area under the curve) 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.

The analyses described in this SAP (Statistical analysis plan) are based upon the following study documents:

- Clinical Study Protocol Amendment 2 (v3.0), dated 03 March 2021
- Electronic Case Report Form (eCRF), Version 1.0 (October 27, 2020)
- AZ Corporate CSRHLD Reporting Standards v3.3
- The following AZ templates:
    - AZ Corporate CSRHLD Tables Templates v3.5
    - AZ Corporate CSRHLD Figures Templates v3.2
    - AZ Corporate CSRHLD Listings Templates v1.4
    - AZ Corporate CSRHLD Reporting Standards v3.3.
    - AZ Respiratory CSR/HLD Figure Template

This SAP details the statistical methodology to be used for analysing the study data and outlines the statistical programming specifications for the tables, listings and figures (TLFs). It describes the variables and analysis sets, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP). The SAP describes the statistical analysis as it is foreseen when the study is being planned if circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made in an updated SAP. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in an SAP Addendum and discussed in the Clinical Study Report (CSR).

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

Objectives	Endpoints/Outcome measures
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
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

Objectives	Endpoints/Outcome measures
Exploratory	
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a randomised, double blind, multi-center, 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 mixed meal tolerance test (MMTT) compared to baseline. Approximately 46 participants with type 2 diabetes mellitus (T2DM) will be randomised 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 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.

Each cohort will be treated for two 72-hour periods in a cross-over design, with a 3-week Wash-out 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 Wash-out (see the Schedule of Activities -SoA-).

There will be three 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):

- **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 Wash-out 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 Wash-out 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 Wash-out period between treatment periods. (N = 8 completed [4 in each sequence group].)

With the exception of the SoA, where the headings of visits 4 and 5 include both the day within the study and within each period (such as 26 and -2 for the same day), all days in this document refer to days within each period. As an illustration, Day 28 in the study is only referred to as Day 1 in this document.

In treatment period 1, participants will be fitted with a continuous glucose monitoring/flash glucose monitoring (CGM/FGM) device on Day -4 on an Out-patient' basis. Within each treatment period, participants will 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.

3.2 Variables associated to the different endpoints.

As stated in section 3.1, Days refer to those within each treatment period (eg, Days 24, 26, 27, 28, 39, 30, 31 in the study referred to as Day -4, -2, -1, 1, 2, 3 and 4).

3.2.1 Pharmacodynamic Variables

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

A CGM/FGM device will be fitted on an Out-patient' basis on Day -4 and removed on Day 4. Mean daily glucose will be determined from multiple measures.

Mixed Meal Tolerance Test (MMTT)

On Days -1 and 4, a standardised mixed meal (meal should be consumed as fast as the participant can, within 30 minutes) will be administered around 07:00 a.m., after an overnight fast of 12 hours. Blood samples will be taken according to the schedule in section 6.2 for analysis of glucose, insulin, C-peptide, Glucagon-like peptide-1 (GLP-1), Glucose-dependent insulin releasing polypeptide (GIP), glucagon and free fatty acids (FFAs).

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

On Days -1 and 3, sodium and potassium concentrations in urine will be measured over 24 hours.

TNFα Concentrations

On Day 3, TNFα concentrations in blood will be measured and analysed with and without stimulation with LPS in Cohorts 1 and 2.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

3.2.2 Safety and Tolerability Variables

Adverse Events and Serious Adverse Events

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

Time Period and Frequency for Collecting AE and SAE Information

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

Serious adverse events will be recorded from the time of signing of the ICF.

Adverse event variables

The following variables will be collected:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity of the AE:
  - 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)

- 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.

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'.

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.

Adverse Events Based on Examinations and Tests

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.

Physical Examinations

A complete examination will include: 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 examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Height and weight

Height and weight will be assessed at the times specified in the SoA. In addition, as detailed in section 3.2.1, weight will be assessed Each time the CCI device is used.

Vital Signs

Vital signs will be assessed after the participant has rested in the supine position for ≥10 minutes at the times specified in the Schedule of Activities:

- 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.

Aural body temperature (ºC) will also be measured.

Electrocardiograms

A 12-lead ECG will be performed after 10 minutes' supine rest at the times specified in the Schedule of Activities. The investigator will interpret the overall results as normal or abnormal and, if abnormal, whether or not it is clinically significant.

The type and nature of abnormalities will be documented whereas clinically significant findings will be recorded as AEs, if applicable.

Additional ECG unscheduled assessments may be performed by the investigator.

As detailed in the eCRF, the following parameters will be assessed in 12-lead ECGs:

RR-interval (msec)

QRS-interval (msec)

QT-interval (msec)

QT-interval corrected using the Fridericia correction formula (QTcF) (msec)

Heart rate (beats per minute [bpm]).

The ECG will be evaluated by the Investigator as 'Normal' or 'Abnormal'.

Clinical Safety Laboratory Assessments

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

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

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

Laboratory Variables

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	Activated partial thrombin time (aPTT)
CCI	

[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 standardised 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).

3.2.3 Pharmacokinetic Variables

Pharmacokinetic analysis for AZD9567 will be performed by Covance Clinical Pharmacokinetic Alliance. Pharmacokinetic parameters will be derived using standard non-compartmental methods using WinNonLin version 8.1 or higher (Certara).

The following PK parameters will be calculated:

- 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.

The following diagnostic parameters will be listed but not summarised:

- λz lower Lower (earlier) t used for λz determination
- λz upper Upper (later) t used for λz determination
- λzN Number of data points used for λz determination
- λz span ratio Time period over which λz was determined as ratio of t½
- Rsq_adj Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

TLFs in the report will be checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

Summary tables will include the results of each planned sequence in the case of the all randomised subjects set (RND), planned treatment in the case of the Full Analysis Set (FAS) or actual treatment in the case of the Safety Analysis Set (SAF), Per Protocol Analysis Set (PP) and the PK Analysis Set (PKAS).

Non-PK continuous data will be summarised in terms of number of observations, the mean, standard deviation (SD), median, 25th and 75th percentiles (where appropriate), minimum, maximum. In the

case of PK data, the Pharmacokinetics section of this SAP lists the statistics included in the summary tables.

For continuous data, the mean, median and geometric mean will be rounded to one additional decimal place compared to the original data. The SD and geometric coefficient of variation (CV) will be rounded to two additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. The maximum number of decimal places reported will be four for any summary statistic.

One decimal will be presented for the geometric CV % included in the PK summary tables.

Categorical data will be summarised in terms of the number of participants, frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator (participants included in the analysis sets or number of non-missing values).

Confidence intervals (CIs) will be presented to one additional place than the original data. P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Unless otherwise noted, for the calculation of a change from baseline, the last reliable assessment (in the case of blood pressure, the average of triplicate assessments) prior to the first dose of each study treatment will be considered the baseline measurement.

In the case of assessments at scheduled timepoints, the post-baseline scheduled or non-scheduled reliable assessment closest to the timepoint will be used. If two post-dose assessments are equidistant from a timepoint, the earlier of the two will be used.

All glucose values will be presented in mmol/L. The following formula will be used for the conversion of glucose concentrations from mg/dL to mmol/L:

Glucose (mmol/L) = Glucose (mg/dL) x 0.0555

All analyses of pharmacodynamics endpoints involving a linear mixed model will be run separately for each cohort.

Change from baseline and percent change from baseline

The change from baseline at each visit will be calculated as:

Change from baseline at visit X = absolute value at visit X-baseline value

The percent change from baseline will be calculated as:

Percent change from baseline = (change from baseline/baseline value) ×100%

If either a visit value or the baseline visit value is missing, the change from baseline value and the percent change from baseline will be set to missing.

4.3 General Variables

4.3.1 Study Day Definitions

Study day 1 is defined as the date of first dose of study treatment within each treatment period. Within each treatment period, for visits (or events) prior to first dose, study day is defined as 'date of visit [event] – date of first dose of study treatment'. For visits (or events) that occur on or after first dose of study treatment, study day is defined as 'date of visit [event] – date of first dose of study treatment + 1'.

"Days since last dose" is defined as 'date of visit [event]– date of last dose of study treatment' where "date of last dose" is defined as the date of dosing immediately preceding the event occurrence.

4.3.2 Handling of Missing Data

Unless otherwise stated, missing data will not be imputed.

4.3.2.1 Imputations of Partial Medication and AEs Dates

There will be no imputation of any incomplete dates.

The following rules will be used to determine whether or not an AE has taken place on-treatment:

1. An AE starting from last dose plus 21 days will be considered on-treatment.
2. An AE with an incomplete start date and whose end date is not prior to the time of dosing on Day 1 will be considered to have taken place on-treatment unless the non-missing components of the incomplete start date indicate that the start date falls outside the time from dosing on Day 1 to last dose plus 21 days.

The following rules will be used to assign concomitance to a medication:

1. Exclusively prior medications are those that started and stopped prior to the first dose of the investigational medicinal product (IMP) in the first treatment period and those that started and stopped after 21 days after the last dose in the first period and before the first dose of IMP in the second period. Medications taken between the first dose and up to 21 days after the last dose in any period are concomitant (including medications that started prior to dosing and continued after)
2. A medication with incomplete start and/or end dates will be considered concomitant unless the non-missing components of the incomplete dates indicate that the intake of the medication did not take place between Day 1 and the last dose plus 21 days.

AEs and medications with completely missing end dates will be assumed to be ongoing.

4.3.3 Imputation Rules for Laboratory Values Outside of Quantification Range

Values of the form "< x" (i.e., below the lower limit of quantification [LLoQ]) or "> x" (i.e., above the upper limit of quantification [ULoQ]) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

4.4 Software Programs

All report outputs will be produced using SAS® version 9.4 in a secure and validated environment. PK analyses will be produced using Phoenix® WinNonLin (WNL) version 8.1 or later in a secure and validated environment.

All report outputs will be provided to the Sponsor. Tables and figures will be combined in one PDF document and listings in another.

4.5 Study Patients

4.5.1 Disposition of Patients

A listing will be created for subjects discontinued from the study using the ENR. An additional listing will be created for subjects completing the study using the RND. Both listings will include the standardised disposition term and the date of disposition event.

A summary table will be created and will include, in addition to the number of patients enrolled, the number and percentage of patients who:

- were randomised
- were not randomised
- received at least a dose of the first treatment
- completed the first treatment
- discontinued the first treatment
- received at least a dose of the second treatment
- completed the second treatment
- discontinued the second treatment
- completed study
- were withdrawn from the study for any reason (one row in the table for all reasons)
- were withdrawn from the study for each reason (one row in the table for each reason).

4.5.2 Protocol Deviations

Important protocol deviations (IPD) may lead to the exclusion of participants from the PP and the PKAS. Deviations will be defined before database lock. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria
- Administration of prohibited concomitant medications expected to influence the primary endpoint
- Receiving incorrect study intervention than randomised to.

All protocol deviations will be discussed at a data review meeting prior to database lock in order to define the analysis sets for the study. All IPDs will be listed by participant.

The Protocol Deviation Specifications will be followed to assess which protocol deviations are important in a Data Review Meeting (DRM) shortly before database lock/unblinding. A DRM report detailing the assessment of protocol deviations, AEs, the assignment of participants to analysis sets and the exclusion of data from specific analyses will be signed by all scientific experts.

The number and percentage of patients in the FAS meeting each IPD criterion will be summarised by cohort. Patients deviating from an IPD more than once will be counted once for that criterion. Any patients who have more than one IPD will be counted once in the overall summary.

The number of enrolled patients included/excluded from each of the analysis sets will be summarised. Patients and data excluded from each analysis set will be listed with the reason (such as the specific IPDs or AEs) for exclusion.

4.6 Analysis Sets

The following sets are defined:

Population/Analysis set	Description
All enrolled subjects (ENR)	All participants who signed informed consent prior to any study-related procedures.
All randomised subjects (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 the 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. The PKAS will be analysed according to the actual treatment.

4.7 Demographics and Baseline Characteristics

Demographic characteristics (age, sex, race, ethnicity, country) and baseline patient characteristics (height, weight and BMI) will be listed and will be summarised by cohort in the SAF and FAS. In

addition to presenting descriptive statistics for age, the summary table will present the number and percentage of patients per age group (18-44, 45-64 and 65-75 years).

4.8 Baseline, change from baseline and percentage change from baseline definitions

Demography and baseline characteristics

For demography and baseline characteristics other than weight, the baseline will be the assessment at screening. For weight, the baseline will be the assessment at Day -1 performed by means of the CCI device. If the weight at Day -1 is missing, the weight at Day -2 (or at Screening, in the case of period 1 if the value at Day -2 is also missing) will be the baseline for such a period.

Pharmacodynamics

Change in AUC(0-4)

In the case of the linear mixed models for the change from baseline in glucose AUC(0-4) (primary endpoint), hormones related to glucose homeostasis (insulin, glucagon, GLP-1, GIP), FFAs and C-peptide (secondary endpoints), the baseline measurement will be the AUC(0-4) on Day -1 (i.e., prior to first dosing) of each period.

Glucose concentrations assessed by CGM

For the calculation of the rise in mean glucose and the mean daily glucose, the baseline will be the average of the values from -24 hours to first dosing on Day 1 (values from -72 to -24 hours will be excluded from the baseline) of each period.

For the MMRM for the rise in mean glucose and the mean glucose, the baseline included as a covariate in the model will be the value -24 hours to first dosing on Day 1 of each period.

MMTT derived first phase insulin response

For the calculation of the change from baseline of insulin, glucose and C-peptide included in the calculation of ΔI10/ΔG10, ΔI30/ΔG30, ΔC10/ΔG10 and ΔC30/ΔG30, the baseline will be value at Day -1 of each period.

24-hour U-Na and U-K

For Na and K and the Na/K ratio, the baseline will be the value at Day -1 in each period.

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Safety

ECG and vital signs

For ECG and vital signs, the baseline will be the pre-dose assessment at Day 1 in each period. If this value is missing the value closest in time prior to Day 1 within the same visit (or at Screening, in the case of period 1) will be the baseline for such a period.

Clinical chemistry/haematology/urinalysis

For the safety laboratory assessments, the baseline for the calculation of the change from baseline will be the pre-dose assessment at Day 1 in each period. If this value is missing, the value closest in time prior to Day 1 within the same visit (or at Screening, in the case of period 1) will be the baseline for such a period.

For the linear mixed models for Na, K and Na/K, the baseline included as covariate will be the same as that used to calculate the change from baseline.

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Serum cortisol and ACTH

For the calculation of the difference in the concentration of each of these hormones between Days -1 and 4 of each period, the baseline will be value on Day -1. If the concentration of ACTH at Day -1 in period 1 is missing, the concentration at the Screening visit will be the baseline for such a period.

4.9 Medical History

The Full Analysis Set will be used for the presentation of the data.

Medical history data will be listed by patient.

A summary of the number and percentage of patients with any relevant medical history will be presented by SOC and PT, by treatment sequence.

Relevant surgical history will be listed in the same manner.

Medical history data of diabetes will be listed by patient including start date and end date or on going.

4.10 Prior and Concomitant Medications, and other treatments

All listings and tables will be based on the Safety Analysis Set.

Medications will be coded using the World Health Organisation-Drug Dictionary (WHODRUG) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

Exclusively prior medications are those that started and stopped prior to the first dose of the investigational medicinal product (IMP) in the first treatment period and those that started and stopped after 21 days after the last dose in the first period and before the first dose of IMP in the second period. Medications taken between the first dose and up to 21 days after the last dose in any period are concomitant (including medications that started prior to dosing and continued after).

Concomitant medication will be listed by participant and will include the reported name, anatomical therapeutic chemical (ATC), route of administration, total dose, frequency, start date/time, duration, whether or not ongoing and indication and will be summarised by ATC and PT.

Medications ongoing during both the periods will be counted under both Period 1 and Period 2.

Prior and concomitant use of Metformin will be listed by participant and will include the total dose, frequency, start date/time, duration and whether or not ongoing and will be summarised by ATC and PT.

The number of subjects taking concomitant medications under each treatment will be summarised by ATC classification/ Generic term.

The duration will be calculated as:

Duration (in days) = (end date – start date) + 1, if only date is known.

4.11 Safety and Tolerability Evaluation

The actual treatment will be used for all safety and tolerability analyses. All listings and tables will be based on the Safety Analysis Set.

The listings of the safety data (AEs, laboratory data, vital signs, and ECG) will include scheduled and unscheduled assessments.

4.11.1 Adverse Events

Within each cohort, AEs will be assigned as having taken place after each of the two treatments if the start of the AE is after the first dose of the treatment but before the end of 21 days after the last dose (i.e., the end of Day 24, in the case of subjects whose last dose was on Day 3). AEs on Day 1 with a missing start time will be assumed to have started after the first dose.

In order to assign the corresponding SOC and preferred term to each AE, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or higher.

AEs occurring prior to the time of dosing on Day 1 and after 21 days after the last dose will not be included in summaries.

An AE listing for the Safety analysis set will cover details for each individual AE. A summary table with the number of AEs, by SOC and PT will be created.

The following summaries for the number and percentage of participants will be created:

- Number of subjects with adverse events in any of these categories:
  - Any AE
  - Any AE with outcome = death
  - Any SAE (including events with outcome = death)
  - Any AE leading to discontinuation of IP
  - Any AE leading to drug interruption
  - Any AE leading to withdrawal from study
- Number of subjects with adverse events, by SOC and PT
- Number of subjects with adverse events, by PT
- Number of subjects with adverse events leading to discontinuation of investigational product, by system organ class and preferred term.

In summaries including SOC or PT, the summaries will first be sorted by decreasing percentage of participants in each SOC and PT within SOC, and then alphabetically by SOC, and PT within SOC.

The following summaries for the number and percentage of adverse will be created:

- Number of adverse events by system organ class and preferred term.

4.11.2 Deaths and Serious Adverse Events

The number of SAEs, by SOC and PT will be summarised.

These summaries will be created for the number of subjects and adverse events, by SOC and PT.

4.11.3 Clinical Laboratory Evaluation

All values will be classified as low (below range), normal (within range), or high (above range) based on central laboratory reference ranges.

The Na/K ratio will be calculated at each timepoint and this ratio will be included in clinical chemistry listings and tables. All clinical laboratory results will be listed.

The comparison of the effect of treatment on changes in Na, K and Na/K will be analysed by means of the same statistical model as that used for the analysis of the primary endpoint.

For haematology, clinical chemistry and coagulation a table with descriptive statistics of absolute values and changes from baseline for each laboratory variable over time. Only planned tests will be summarized. In the case of the urinalysis, individual measurements will be listed and a summary table

of the baseline versus maximum value on-treatment (ie, a shift table) will be created.

The on-treatment definition will be based on the on-treatment definition used for AE.

4.11.4 Vital Signs, ECGs

Vital Signs

Vital signs data will be listed by participant including changes from baseline. Flags for a clinically significant assessment will be provided in the listing.
Descriptive statistics for absolute values and changes from baseline will be presented by treatment and by cohort.

ECGs

All ECG parameters will be listed by participant including changes from baseline for numeric ECG parameters. Abnormalities in ECG will also be listed.
Descriptive statistics for absolute values and changes from baseline will be presented by treatment and cohort. The on-treatment definition will be based on the on-treatment definition used for AE.
The number and percentage of participants under each treatment exceeding the following ICH boundaries of QTcF will be tabulated:

- Absolute value > 450 msec and > 480 msec
- Increase from baseline > 30 msec and > 60 msec.

This summary table will also include the number and percentage of participants under each treatment exceeding the following values:

- Absolute value >450 msec and Increase from baseline >30 msec
- Absolute value >500 msec and Increase from baseline >60 msec.

The following figure will be provided for each ECG parameter:

- Box-plot by treatment and day

4.11.5 Morning serum cortisol and ACTH

The morning serum cortisol and ACTH will be listed and tables with descriptive statistics for the value -15 minutes prior to the mixed meal on Days -1 and 4 (in each period) and change from baseline will be created.

4.12 Pharmacodynamics and Pharmacokinetics

4.12.1 Analysis and Data Conventions

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

The null hypothesis for the primary analysis is:

> H_0: there is no difference in the change in glucose AUC(0-4) versus baseline in AZD9567 compared to prednisolone following a standardised MMTT.

The alternative hypothesis for the primary analysis is:

> H_a: there is a difference in the change in glucose AUC(0-4) versus baseline in AZD9567 compared to prednisolone following a standardised MMTT.

In order to test the null hypothesis, a main analysis involving the FAS will be conducted. If more than 10% of participants receive the wrong treatment, a sensitivity analysis involving the PP will be conducted.

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)

As this is a Phase 2a study, no adjustments for multiple testing will be performed.

4.12.1.1 Multi-center Studies

No adjustments for center will be performed.

4.12.1.2 Handling of Dropouts or Missing Data

Summary statistics will be based on non-missing values.

4.12.1.3 Interim Analyses

Two interim analyses are planned.

The first interim analysis will be conducted when 50% of the participants in Cohort 1 have completed the study. The purpose of the first interim analysis is to evaluate the feasibility of the assumptions and conduct sample size re-estimation if required.

The main objective of the first interim analysis is to report the statistical analyses involving the first endpoint, the secondary endpoints related to glucose (mean daily glucose at 48-72 hours treatment and rise in mean daily glucose over 24-hour periods from start of IMP dosing) and the safety endpoints (AEs/SAEs) for 50% of the subjects in Cohort 1.

The second interim analysis will be conducted when all the participants in Cohort 1 have completed the study. The main objective of the second interim analysis is to report the statistical analyses involving all subjects in Cohort 1.

The second interim analyses will not include PK data.

4.12.2 Pharmacodynamics

All the models presented in this section will be analysed with unstructured covariance structure used for the within-participant errors. In the case of a model which does not converge, the analysis will be performed with a Toeplitz covariance structure and, in case of non-convergence, it will be performed with a compound symmetry structure.

Primary endpoint

The primary endpoint is the change in glucose AUC(0-4) and will be summarised by timepoint (baseline and Day 4) and by each cohort. The comparison of the change in glucose AUC(0-4) (where change from baseline in glucose AUC is assumed to be normally distributed) between the two treatments administered within each cohort after a standardised MMTT will be performed by means of two linear mixed effects models, with an unstructured covariance structure, with treatment, period and sequence as fixed effects, participant within sequence as random effect and baseline as covariate.

Two models will be run separately for each cohort:

1. In the first model, the dependent variable will be the change from baseline in AUC(0-4) whereas the AUC(0-4) on Day -1 will be included as a covariate. The treatment effects will be estimated by the Least Square means (LS means) and their 95% CIs and the difference between the two treatments by the difference in LS means with its 95% CI.

2. The second model will involve the following three steps:
   a) Log-transformation of the AUC(0-4):

      First, the AUC(0-4) in Day -1 and the AUC(0-4) in Day 4 will be log-transformed. The log-transformed AUC(0-4) in Day -1 will then be subtracted from the log-transformed AUC(0-4) in Day 4 to calculate the change in AUC (0-4) in log units.
   b) Execution of the model:

      The model will include the change in AUC (0-4) in log units as a dependent variable and the log-transformed AUC(0-4) in Day -1 as covariate.
   c) Back-transformation of the results from the model:

      The results from the execution of the model will be back transformed to the original scale after an exponentiation of the means and CIs estimated by the model to obtain the percentage geometric LS means of the treatments and their percentage SEs. The LS mean difference and its CI between the two treatments will also be back-transformed to yield the percentage geometric mean ratio between the two treatments with its 95% CI at Day 4.

The statistics for the percentages geometric LS means, percentage SE, percentage geometric LS mean ratio and percentage 95% CI will be calculated as follows:

i) Percentage geometric LS mean = (exp(estimate)-1)*100 where estimate is the natural log of LS mean

ii) Percentage SE = sqrt(exp(2*estimate)*SE^2)*100

iii) Percentage geometric LS mean ratio= (exp(estimate)-1)*100 where estimate= log LS mean difference

iv) percentage 95% CI lower and upper: (exp(lower)-1)*100; (exp(upper)-1)*100.

If more than 10% of participants are treated erroneously, a sensitivity analysis will be carried out using the actual treatment received instead. Descriptive statistics and graphical presentations will be presented.

The following graphs will be provided:

- Line plot: the Mean glucose levels (MMTT) by sampling time in minutes by treatment -visit day; (per cohort)
- AUC(0-4) change from baseline (MMTT) for glucose level by visit day of linear mixed model (Full Analysis Set) (all cohorts in a single plot)

- AUC(0-4) percentage change from baseline (MMTT) for glucose level by visit day linear mixed model (Full Analysis Set) (all cohorts in a single plot).

The following comparison will be performed by the execution of a linear mixed effects model in each case:

- 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).

Secondary endpoints

Mean daily glucose at 48-72 hours (CGM)

The Mean daily glucose (CGM) as well as the change from baseline will be summarize by timepoint (baseline, 00-24 h, 24-48 h and 48-72 h) and by treatment group.

The comparison of the effect of the two treatments on the mean daily glucose at 48-72 measured by CGM will be analysed by means of repeated measures mixed model (MMRM) with treatment + time (0-24h, 24-48h, 48-72h), treatment*time, period and sequence as fixed effects with baseline (mean glucose at -24-0 hours) as covariate and participants within sequence as random effect. Two models will be run separately for each cohort and will be:

1. In the first model, the dependent variable will be the mean daily glucose whereas the mean glucose at -24-0 hours will be included as covariates. The treatment effects will be estimated as described in the first model for the primary endpoint.
2. The second model will involve a log-transformation of both the mean glucose at 0-24, 24-48 and 48-72 hours and the mean glucose at -24-0 hours will be included as a covariate. The treatment effects will be estimated as described in the second model for the primary endpoint.

The following graphs will be provided:

- Glucose mean levels (CGM) at 0-72 h by treatment (per cohort)
- Glucose mean levels (CGM) at 0-72 h by treatment (all cohorts in a single plot).

Rise in mean glucose at 00-24 h, 24-48h and 48-72 h (CGM)

The comparison of the effect of the two treatments on the rise in mean glucose at 0-24, 24-48 and 48-72 hours will be performed following two different approaches:

1) In the first approach three different models will be performed:

i) Change at 00-24 h from baseline (24 hours of CGM prior to dosing) performed by means of mixed models with treatment, period and sequence as fixed effects, participants within sequence as random effect and baseline mean glucose

ii) Change at 24-48 h from baseline (24 hours of CGM prior to dosing) performed by means of mixed models with treatment, period and sequence as fixed effects, participants within sequence as random effect and baseline mean glucose

iii) Change at 48-72 h from baseline (24 hours of CGM prior to dosing) performed by means of mixed models with treatment, period and sequence as fixed effects, participants within sequence as random effect and baseline mean glucose.

2) In the second approach three different models will be performed:

i) Change at 00-24 h from baseline (24 hours of CGM prior to dosing) performed by means of mixed models with treatment, period and sequence as fixed effects, participants within sequence as random effect and baseline mean glucose

ii) Change at 24-48 h from baseline (00-24 h) performed by means of mixed models with treatment, period and sequence as fixed effects, participants within sequence as random effect and baseline mean glucose

iii) Change at 48-72 h from baseline (24-48h) performed by means of mixed models with treatment, period and sequence as fixed effects, participants within sequence as random effect and baseline mean glucose.

The three models for each of the approaches were repeated considering the log-transformation of the dependent variable to obtain the Geometric LS means and the Geometric LSMean Ratio (%).

The following comparison will be performed for the change and the percent change from baseline at 0-24, 24-48 and 48-72 hours:

- 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).

The following graphs will be provided:

- Rise in mean change from baseline (CGM) for glucose by Days (Day -1 (24 h prior to dosing), Day 1 (00-24 h), Day 2(24-48 h), Day 3(48-72 h)) 1st approach (per cohort)

- Rise in mean change from baseline (CGM) for glucose by Days (Day -1 (24 h prior to dosing), Day 1 (00-24 h), Day 2(24-48 h), Day 3(48-72 h)) 2nd approach (all cohorts in a single plot)
- Rise in mean percentage change from baseline (CGM) for glucose by Days (Day -1 (24 h prior to dosing), Day 1 (00-24 h), Day 2(24-48 h), Day 3(48-72 h)) 2nd approach (all cohorts in a single plot).

Change from baseline in fasting glucose

The comparison of the effect of the two treatments on the change from baseline in fasting glucose (-15 minutes) between Days -1 and 4 will be performed by the same model as that for the comparison of the primary endpoint.

The following comparison will be performed for the change and the percent change from baseline at Day 4:

- 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).

Changes in in AUC(0-4) in hormones, FFAs and C-peptide in response to a MMTT

The comparison of the effect of treatment on changes in insulin, glucagon, GLP-1, GIP, FFAs and C-peptide will be analysed as the primary endpoint.

The following graphs will be provided for each of the variable with the exception of C-peptide:

- The changes from baseline at different timepoints by treatment (all cohorts in a single plot)
- The percentage changes from baseline at different timepoints by treatment (all cohorts in a single plot).

MMTT derived first phase insulin response

The ratio between variables will be calculated based on the following steps:

i) Calculate ΔI10= difference in I (insulin) values between 10 and 0 minutes at Day -1 and Day 4 of each period

ii) Calculate ΔG10= difference in G (glucose) values between 10 and 0 minutes at Day-1 and Day 4 of each period

iii) Calculate the ratio ΔI10/ ΔG10 at Day-1 and Day 4 of each period.

The same steps i) to iii) accordingly to timepoints 10 and 30, will be performed for ΔC10/ΔG10, ΔI30/ΔG30, and ΔC30/ΔG30.

The comparison of the effect of the two treatments on the change in ΔI10/ΔG10 and ΔI30/ΔG30, between Days -1 and 4 will be performed by the same model as that for the comparison of the primary endpoint.

The following comparison will be performed for the change from baseline and the percent change from changes from baseline at Day 4 at 10 and 30 minutes:

- 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).

The previous analyses will be repeated for the comparison of the effect of the two treatments on the change in ΔC10/ΔG10, ΔC30/ΔG30 using C-peptide instead of insulin in the calculation of these ratios.

HOMA-IR and HOMA-S

A summary of the baseline HOMA-IR and HOMA-S and at Day 4 as well as change from baseline, will be provided by treatment.

24-hour U-Na and U-K

The 24-hour Na and K concentration and its ratio (Na/K) in urine will be analysed as the primary endpoint.

The following comparisons will be performed for the change and percentage change from baseline at 0-24 hours on Day 3:

- 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).

TNFα concentrations

Descriptive statistics will be tabulated for the individual measurement points of the LPS-stimulated TNFα levels.

An ANOVA model with treatment, sequence and subject as random effect will be run separately for each cohort (Cohort 1 and Cohort 2) for the comparisons of the treatments at Day 3.

A scatter plot of individual plasma concentrations of AZD9567 (nmol/L) in a log scale on the X axis versus individual LPS-Stimulated TNFα Levels (ng/L) in log scale on the Y axis will be created.

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Calculations of endpoints analysed by statistical models

Calculation of changes from baseline AUC (0-4)

The calculation of the change in glucose, insulin, C-peptide GLP-1, GIP, glucagon and FFAs AUC(0-4) will involve the following steps:

1. The AUC(0-4) each day when the MMTT is consumed will be calculated by means of the linear-log trapezoidal method, i.e., using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

   Accordingly, for a given time interval ($t_1 - t_2$), the AUC could be calculated as follows:

   i) by the linear trapezoidal method:

   $$AUC = 1/2\ (C_1 + C_2)\ (t_2 - t_1)$$

   ii) by the logarithmic trapezoidal method:

   $$AUC = [(C_1 - C_2)\ /(\ln(C_1) - \ln(C_2))]\ (t_2 - t_1)$$

   where:

- C_1 and C_2 are the concentrations at times 1 (t_1) and 2 (t_2).the first time interval ($t_1 - t_2$) is equal to t_1 (ie, the concentration at -15 minutes is assumed to be the same as if it had been made at 0 minutes),
- for assessments at 10, 20, 30, 60, 75, 120 and 180 minutes, t_1 and t_2 are actual times,
- for the planned assessment at 240 minutes, the planned time (240) will be used if such an assessment has been performed within the allowed time window (±5 minutes).

The total AUC between 0 and 240 minutes will be calculated as the sum of the AUC for each of the intervals described in i) and ii).

The total AUC between two time points will be calculated as the sum of the AUCs calculated for each of the intervals between the two time points.

2. The change in AUC(0-4) will be calculated as:

$$\Delta \text{ AUC(0-4)} = \text{AUC(0-4) at Day 4 - AUC(0-4) at Day -1}$$

For the calculation of MMTT $AUC_{0\text{-}4hr}$, the pre-meal measurement (at -15 min) value will be treated as the value at the meal time (0 minutes). The actual time span for each post-meal measure will be calculated starting from the meal time (0 minutes). If any actual sample collection times are missing, use the scheduled nominal times with reference to the actual meal time to impute.

If the actual sampling times differ from the nominal times more or equal to | 5| min, this will be deemed on case-by-case basis if should be considered protocol deviation.

If greater than 50% of scheduled measures are missing, the AUC will be set as missing; if the first two or last two scheduled measures are both missing, then the AUC will also be set as missing; otherwise:

For all the MMTT endpoints (glucose, insulin, glucagon, GLP-1, GIP, FFAs and C-peptide):

If any interior measures are missing, the trapezoid rule can be used to calculate the AUC by ignoring the missing time point: i.e. The missing timepoint X will be imputed with the value obtained considering the linear interpolation between the last actual assessment taken prior to point X, and the first actual assessment taken after point X.

For glucose MMTT endpoint:

- If the pre-meal value is missing, set the missing value = 92% of the value for next scheduled time point.
- If the last value is missing, set the missing value = 87% of the value for the time point that is scheduled immediately prior to the last time point.

For the rest of MMTT endpoints (insulin, glucagon, GLP-1, GIP, FFAs and C-peptide):

- If the pre-meal value is missing, set AUC = missing
- If the last value is missing, set AUC = missing

AUC(0 -4h) calculation assumes that measurements are available at 240 min exactly. Deviation from 240 min will induce a systematic overestimation of the actual value of the sampling time is used exceeds 240 min and underestimation of the actual time is under 240 min. If the deviation is within the allowance window (± 5 min) the sampling time will be equated to 240 min. If the sampling time for the 240 min measurement is out of the sampling window (± 5 min) a linear interpolation will be considered to assess the value at 240 min using the actual sampling times for the 180 min and the 240 min measurements.
Actual time point (at 180 min) and the time point for last sampling will be defined with t_{180} and with t_{last} respectively, and the values of the endpoint (glucose, insulin etc) at the actual measured timepoint and at time point for the last sampling will be defined with y_{180} and y_{last}. From the available information (t_{180}, y_{180}), (t_{last}, y_{last}) the value at t_{240} , i.e. the value that the endpoint would have if we would have taken the sample at exactly 240 min form start will be interpolated. Interpolation assumes a linear equation with slope

$$m = (y_{last}-y_{180})/(t_{last}-t_{180})$$

and intercept

$$b = \text{mean}(y_{last};y_{180})- m*\text{mean}(t_{last};t_{180})$$

giving the value at 240 minutes of:

$$y240 = b + m*240.$$

The 92 % and 87 % correction factors were based on the MEDI0382 (D5670C00007) study.

Calculation of HOMA-IR

The HOMA-IR will be calculated as follows based on glucose and insulin measured prior to MMTT (-15 min):

$$\text{HOMA} - \text{IR} = \frac{Glucose\ \left(\frac{mmol}{L}\right)\ \text{x Insulin (mU/L)}}{22.5}$$

HOMA-S will be calculated as the reciprocal of HOMA-IR.

4.12.3 Pharmacokinetics

4.12.3.1 Concentrations

Plasma concentrations of AZD9567 will be listed by actual and relative (to dose administration) sampling time. The following summary statistics will be presented for these concentrations at each time point by treatment and cohort:

- n below the lower limit of quantification (LLOQ) (only for concentrations)
- Geometric Mean
- Geometric CV%
- Geometric Mean - SD
- Geometric Mean + SD
- Arithmetic Mean
- Arithmetic SD
- Median
- Minimum
- Maximum

In listings, concentrations less than the lower limit of quantification (LLOQ) will be presented as below the lower limit of quantification (BLQ). In listings and tables where the terms BLQ or LLOQ are included, the LLOQ (numerical value) will be included in a footnote.

For the calculation of statistics, concentrations that are BLQ will be handled as follows at each time point:

- If ≤50% of the concentrations are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- If >50%, but not all, of the concentrations are BLQ, the arithmetic mean, arithmetic CV, arithmetic mean, and arithmetic SD will be reported as 'NC' (not calculable). The maximum value will be reported from the individual data, and the minimum and median will be set as 'BLQ'.
- If all concentrations are BLQ, no descriptive statistics will be calculated. 'NA' (not applicable) will be presented for geometric CV, and arithmetic SD, and 'BLQ' will be presented for geometric mean, arithmetic mean, median, minimum, and maximum.

For PK concentration and parameter data, if there are <3 values available at a time point, only the maximum, minimum, and n will be reported; the remaining descriptive statistics will be reported as 'NC'. Concentrations that are BLQ are considered a value.

Post-dose concentrations where the actual time deviation deviates more than 10% from the scheduled time will be excluded from summaries by planned time point.

Missing samples will be reported as no sample ("NS") and excluded from analysis.

Source data shall be used in all derived PK concentrations without prior rounding

The following figures, will be generated for each IMP by Cohort:

- Individual Subject Profiles, Plasma Concentration-time Data - Linear Scale: both days on 1 plot
- Individual Subject Profiles, Plasma Concentration-time Data - Semi-Logarithmic Scale : both days on 1 plot
- GMean, Plasma Concentration-time Data - Linear Scale: both days on 1 plot
- GMean, Plasma Concentration-time Data - Semi-Logarithmic Scale: both days on 1 plot.

In combined figures displaying subject profiles, all subjects will be included in the same figure and concentrations will be displayed by actual sampling time. In figures displaying mean concentrations, mean concentrations will be displayed by time point.

4.12.3.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated following these guidelines:

Pharmacokinetic analysis will, where possible, be calculated using times recorded in the raw data. If actual times are missing, nominal times may be used.

The concentrations reported by the analytical laboratory for PK analysis will be used in all the analyses. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

Cmax and tmax will be obtained directly from the plasma concentration-time profiles. For multiple peaks, the highest post-dose concentration will be reported as Cmax. In the case that multiple peaks are of equal magnitude, the earliest tmax will be reported.

Concentrations BLQ from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to zero with the following exceptions:

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be set to missing, unless there is a scientific rationale not to do so, which will be documented by the pharmacokineticist.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a pre-dose concentration is missing, these values may be set to zero by default.

The terminal elimination rate constant (λz) will be calculated by log-linear regression of the terminal portion of the concentration-time profile. The following will be considered:

- If more than one phase is present only data points from the terminal phase will be used.
- A minimum of 3 data points after Cmax, including the last measurable concentration, will be used for calculating λz.
- Where the elimination half-life is estimated over less than 3 times the subsequently estimated terminal half-life the robustness of the $t_{½\lambda}$ estimate will be discussed in the CSR.
- Rsq adjusted should be greater than 0.8. Where Rsq adjusted < 0.8, half-life and half-life dependent parameters may be excluded from summary statistics and statistical analysis with sponsor agreement.

The AUCs will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal rule when concentrations are decreasing (linear up log down). The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the LLOQ.

Generally, data should not be excluded from analysis. However, where this is scientifically merited a sensitivity analysis may be performed and the data will be discussed in the CSR.

Pharmacokinetic summaries will be based upon the PKAS.

Pharmacokinetic parameters will be listed by subject and summarised by treatment. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum values. For tmax, only median, minimum and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings for PK parameters:

- Individual PK parameters will be presented to four significant digits, with the exception of tmax, which will be presented to two decimal places.
- Parameters derived directly from source data (e.g. Cmax,) shall be reported with the same precision as the source data (if this is not four significant digits).
- The mean, geometric mean, median and SD values will be reported to four significant digits, all other descriptive statistics will be reported to three significant digits except for CV% which will be presented to one decimal place.
- For tmax the minimum and maximum will be presented to two decimals places and all other descriptive statistics will be presented to three decimal places.

4.13 Other Analyses

Not applicable.

4.14 Determination of Sample Size

CCI [redacted]

CCI [redacted]

4.15 Changes in the Conduct of the Study or Planned Analysis

The following changes to the statistical methodology planned in Study Protocol will be applied:

- The repeated measures mixed model will also include the time term.

5 REFERENCES

van Genugten RE, van Raalte DH, Muskiet MH, Heymans MW, Pouwels PJW, Ouwens DM, et al. Does dipeptidyl peptidase-4 inhibition prevent the diabetogenic effects of glucocorticoids in men with the metabolic syndrome? A randomised controlled trial. Eur J Endocrinol. 2014 Feb 4;170(3):429-39.

Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014 Dec 19;14:135.

6 APPENDICES

6.1 Schedule of Activities

Visit	1	2	Visit 3 [a]						Wash-out (3 weeks) [b]	4	Visit 5 [a]						6	Comments (all sections refer to the CSP)
Phase	Screening	Out-patient visit	Residency in Unit [a]							Out-patient 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]							Sections 5.1 and 5.2
COVID-19 symptom telephone screening	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							Section 5.3.2
Alcohol breath test	X		X								X							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
Randomisation in IVRS			X															

Visit	1	2	Visit 3 [a]						Wash-out (3 weeks) [b]	4	Visit 5 [a]						6	Comments (all sections refer to the CSP)
Phase	Screening	Out-patient visit	Residency in Unit [a]							Out-patient 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)		
Adverse events		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	Section 6.5 and Appendix F
BLOOD SAMPLE COLLECTION																		
Haematology	X		X		X			X			X		X			X	X	Section 8.3.4
Clinical chemistry (including trigycerides and HDL-C)	X		X		X			X			X		X			X	X	Section 8.3.4
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
TNFα j							X								X			Pre-dose Post-dose 1, 2, 4, 8, 12, 24 hours [k] Section 8.2.1.4
PK (AZD9567)							X	X							X	X		Pre-dose Post-dose 5, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30 hours [k] Section 8.6.1

Visit	1	2	Visit 3 [a]						Wash-out (3 weeks) [b]	4	Visit 5 [a]						6	Comments (all sections refer to the CSP)
Phase	Screening	Out-patient visit	Residency in Unit [a]							Out-patient 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)		
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
MMTT				X				X				X				X		A standardise d 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 (Section 5.3.1) for analysis of plasma glucose, insulin, C-peptide, GLP-1, GIP, glucagon and FFAs, Sections 1.3.1, and 8.2.1.2
Serum cortisol				X			X	X				X			X	X	X	Sample to be taken at 0800

Visit	1	2	Visit 3 [a]						Wash-out (3 weeks) [b]	4	Visit 5 [a]						6	Comments (all sections refer to the CSP)
Phase	Screening	Out-patient visit	Residency in Unit [a]							Out-patient 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			X	X	X	Sample to be taken at 0800
CCI				X			X	X				X			X	X	X	Sample to be taken at 0800
ACTH	X			X			X	X				X			X	X	X	Fasted sample to be taken at 08:00
CCI				X			X					X			X			Section 8.2.1.5
URINE SAMPLE COLLECTION																		
Urine drug screen (dipstick)	X		X								X							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 8.2.1.3
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.

Visit	1	2	Visit 3 [a]						Wash-out (3 weeks) [b]	4	Visit 5 [a]						6	Comments (all sections refer to the CSP)
Phase	Screening	Out-patient visit	Residency in Unit [a]							Out-patient 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)		
CGM/FGM		X[1]	X	X	X	X	X			X[1]	X	X	X	X	X			CGM/FGM will be fitted on an Out-patient' basis on Day -4 and removed on Day 4, Section 8.2.1.1
Standardise d dinner			X				X				X				X			A standardise d 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) Section 6

a Treatment period 1: Day -4 to Day 4. Treatment period 2: Day 24 to Day 31.
b Wash-out 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 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 24 hours 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 wash-out 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 CGM/FGM will be fitted on Day -4 to enable 72-hour CGM will be taken at baseline.

Note: Interim telephone visits may occur at any time during the Out-patient' 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 normalised ratio; IVRS: Interactive Voice 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: tumor necrosis factor alpha; U-K: urinary potassium; U-Na: urinary sodium.

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

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

GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulin releasing polypeptide.

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