Clinical Study Report Synopsis	
Drug Substance	AZD9567
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A Phase IIa, 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

Study dates: First Subject Enrolled: 26 November 2020
Last Subject Last Visit: 09 June 2021
The analyses presented in this report are based on a clinical data lock date of 16 August 2021

Phase of development: Therapeutic; exploratory (II)

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This study was performed in compliance with International Council for Harmonisation Good Clinical Practice, including the archiving of essential documents.

Study Centres

This study was conducted in Germany and included 3 clinical research units (CRUs) that randomised at least 1 patient each.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints/Outcome Measures
Primary	
To determine the PD effect of AZD9567 on glucose homeostasis compared to prednisolone	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 to 72 h treatment as determined from multiple measures via the CGM system • Rise in mean daily glucose over 24-h periods from start of IMP dosing (00 to 24 h, 24 to 48 h, 48 to 72 h)
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 (ΔI10/ΔG10, ΔI30/ΔG30, ΔC10/ΔG10, ΔC30/ΔG30 – where, Δ: change from baseline, I: insulin, C: C-peptide, G: glucose) • HOMA-IR and HOMA-S
To determine the effect of AZD9567 on U-Na and U-K excretion compared to prednisolone	• 24-h 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 [a]	• 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

Objectives	Endpoints/Outcome Measures
	• Morning serum cortisol • ACTH
Exploratory	
CCI [a]	• CCI
CCI	• CCI • CCI • CCI
CCI	• CCI

[a] Results are reported outside of this CSR.

Abbreviations: ACTH: Adrenocorticotropic hormone; AE: Adverse event; AUC(0-4): Area under the plasma concentration versus time curve from zero to 4 h post-dose; CGM: Continuous glucose monitoring; CSR: Clinical study report; ΔC10: Difference in C-peptide values between 10 and 0 minutes; ΔC30: Difference in C-peptide values between 30 and 0 minutes; ΔG10: Difference in glucose values between 10 and 0 minutes; ΔG30: Difference in glucose values between 30 and 0 minutes; ΔI10: Difference in insulin values between 10 and 0 minutes; ΔI30: Difference in insulin values between 30 and 0 minutes; CCI ; ECG: Electrocardiogram; FFA: Free fatty acid; GIP: Glucose-dependent insulin releasing polypeptide; GLP-1: Glucagon-like peptide-1; HOMA-IR: Homeostatic model assessment-insulin resistance; HOMA-S: Homeostatic model assessment-insulin sensitivity; IMP: Investigational medicinal product; LPS: Lipopolysaccharide; MMTT: Mixed meal tolerance test; PD: Pharmacodynamics; PK: Pharmacokinetics; SAE: Serious adverse event; TNFα: Tumour necrosis factor alpha; U-K: Urinary potassium; U-Na: Urinary sodium.

Study Design

- This was a randomised, double-blind, multi-centre, double-dummy, 2-way cross-over study in patients with type 2 diabetes mellitus (T2DM) 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 area under the plasma concentration versus time curve (AUC) following the standardised mixed meal tolerance test (MMTT) compared to baseline.
- There were 3 separate, 2-way cross-over cohorts, with 3 different dose combinations (72 mg AZD9567/40 mg prednisolone, 40 mg AZD9567/20 mg prednisolone, and placebo/5 mg prednisolone). Patients with T2DM who met all eligibility criteria were randomised in a ratio of 1:1 to a cohort and sequence group as detailed below. Each cohort was treated for two 72-h periods in a cross-over design, with a 3-week washout period between treatment periods.
  - Cohort 1: Patients were randomised in a ratio of 1:1 to receive 72 mg AZD9567 followed by 40 mg prednisolone or 40 mg prednisolone followed by 72 mg AZD9567 (planned N = 24 completed [12 in each sequence group]).
  - Cohort 2: Patients were randomised in a ratio of 1:1 to receive 40 mg AZD9567 followed by 20 mg prednisolone or 20 mg prednisolone followed by 40 mg AZD9567 (planned N = 8 completed [4 in each sequence group]).

  - Cohort 3: Patients randomised in a ratio of 1:1 to receive placebo followed by 5 mg prednisolone or 5 mg prednisolone followed by placebo (planned N = 8 completed [4 in each sequence group]).

- AZD9567 was administered once daily as an oral suspension at 2 dose levels (40 mg/day and 72 mg/day). Prednisolone capsules were administered orally at 3 different dose levels (5 mg/day, 20 mg/day, and 40 mg/day). Since the investigational medicinal products (IMPs) had different formulations, they were administered in a double-dummy fashion, with each patient taking both oral suspension and capsules of prednisolone/placebo.

Target Subject Population and Sample Size

The key inclusion criteria were as follows: Male and female patients 18 to 75 years of age, inclusive; diagnosis of T2DM for 6 months prior to screening; haemoglobin A1c (HbA1c) in the diabetes range or fasting plasma glucose 126 to 220 mg/dL; on stable metformin therapy for at least 4 weeks, where no significant dose change (increase or decrease ≥ 500 mg/day) occurred prior to screening and HbA1c 6% to 9.5%, or on dual therapy with metformin in combination with sodium-glucose co-transporter-2 inhibitor (SGLT2i) or dipeptidyl peptidase 4 inhibitor (DPP4i) and HbA1c 6% to 8%. Patients on dual therapy required 2 weeks washout of SGLT2i or DPP4i.

Approximately 46 patients were planned to be randomised into the study, with the expectation to achieve 40 evaluable patients completing the study.

Investigational Product and Comparators: Dosage, Mode of Administration, and Batch Numbers

The IMPs in this study were AZD9567, prednisolone (comparator), placebo for AZD9567, and placebo for prednisolone.

Table S2 Study Treatments

	AZD9567	Prednisolone	Placebo	
Intervention Name	AZD9567 oral suspension	Prednisolone (modified comparator)	Placebo for AZD9567 oral suspension	Placebo for prednisolone
Dose Formulation	Oral suspension	Capsule	Oral suspension	Capsule
Unit Dose Strength	4 mg/mL	5 mg	-	-
Dosage Level	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 (Cohorts 1, 2, and 3)	Placebo for 3 consecutive days of each treatment period (Cohorts 1, 2, and 3)
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Active comparator	Placebo	Placebo
Batch/Lot Numbers	Provided in Appendix 16.1.6 of the CSR			
Sourcing	Provided centrally by AstraZeneca			
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 a study-specific label

Abbreviations: CSR: Clinical study report.

Duration of Treatment

In this cross-over study, each cohort was treated for two 72-h periods, with a 3-week washout period between treatment periods. The total length of patient engagement (from screening to follow-up) was approximately 79 days.

Statistical Methods

General Principles:

- Non-pharmacokinetic (PK) continuous data were summarised in terms of number of observations, mean, standard deviation (SD), median, 25th and 75th percentiles (where appropriate), minimum, and maximum. Categorical data were summarised in terms of the number of patients, frequency counts, and percentages.
- This study aimed to demonstrate that AZD9567 improves glucose homeostasis compared to oral prednisolone.
  - The null hypothesis for the primary analysis was:

H_0: there was no difference in the change in glucose area under the plasma concentration versus time curve from zero to 4 h post-dose (AUC[0-4]) versus baseline in AZD9567 compared to prednisolone following a standardised MMTT.

– The alternative hypothesis for the primary analysis was:

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

- The following comparisons were 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 was a Phase IIa study, no adjustments for multiple testing were performed. CCI [redacted] No adjustments for centre were performed. Summary statistics were based on non-missing values.

Analysis Sets:

- All Enrolled Participants (ENR): All participants who signed the informed consent form prior to any study-related procedures.
- All Randomised Participants (RND): All participants in the ENR randomised to 1 of the 2 sequence groups within a cohort. The ENR was analysed according to the planned sequence or treatment.
- Full Analysis Set (FAS): All participants in the RND who received at least 1 dose of study intervention. The FAS was analysed according to the planned treatment and used as the primary population for reporting pharmacodynamics (PD) data and to summarise baseline characteristics. Any important deviations from randomised treatment were listed and considered when interpreting the PD data.
- Safety Analysis Set (SAF): All participants in the RND who received at least 1 dose of study intervention. The SAF was 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 was analysed according to the actual treatment received.
- Pharmacokinetic Analysis Set (PKAS): All participants in the FAS with at least 1 quantifiable AZD9567 concentration and no important protocol deviations, or adverse events (AEs) considered to have an effect upon PK. Participants were excluded from the PK population if they had an AE of vomiting before 2 × the median time to reach maximum observed drug concentration (tmax) of the group. Participants in the PKAS were analysed according to the actual treatment.

Statistical Analyses:

- Primary endpoint analysis: The primary PD endpoint, ie, the change in glucose AUC(0-4), was summarised by time point (baseline and Day 4) and by cohort. The comparison of the change from baseline in glucose AUC(0-4) between the 2 treatments administered within each cohort after a standardised MMTT was performed by means of 2 linear mixed effects models with an unstructured covariance structure, with treatment, period, and sequence as fixed effects, patient within sequence as random effect, and baseline as covariate. The 2 linear mixed effects models were run separately for each cohort. In the first model, the dependent variable was the change from baseline in AUC(0-4), whereas the AUC(0-4) on Day -1 was included as a covariate. The treatment effects were estimated by the least-squares (LS) means and their 95% confidence intervals (CIs) and the difference between the 2 treatments by the difference in LS means with its 95% CI. The second model involved 3 different steps and the statistics for the percentages geometric LS means, percentage standard error, percentage geometric least-squares mean ratio, and percentage 95% CI were calculated. The second model was run on a geometric scale and estimates were retransformed to percentages. The PD data were listed by cohort/patient and summarised by planned treatment sequence based on the FAS.
- Secondary endpoint analyses:
  - Mean daily glucose at 48 to 72 h (measured by continuous glucose monitoring [CGM]): The mean daily glucose (measured by CGM), as well as the change from baseline, was summarised by time point (baseline, 00 to 24 h, 24 to 48 h, and 48 to 72 h) and by treatment group. The comparison of the effect of the 2 treatments on the mean daily glucose at 48 to 72 h measured by CGM was analysed using a mixed model repeated measures analysis with treatment + time (00 to 24 h, 24 to 48 h, 48 to 72 h), treatment*time, period, and sequence as fixed effects, with baseline (mean glucose at -24 to 00 h) as covariate, and patients within sequence as random effect. Two models were run separately for each cohort; one considered the mean daily glucose as dependent variable and the other considered a log-transformation of the mean glucose.
  - Rise in mean glucose at 00 to 24 h, 24 to 48 h, and 48 to 72 h (measured by CGM): The comparison of the effect of the 2 treatments on the rise in mean glucose at 00 to 24 h, 24 to 48 h, and 48 to 72 h was performed based on 2 different approaches by means of mixed models with treatment, period, and sequence as fixed effects. In the first approach, the baseline value was average of CGM values from -24 h to 00 h for 3 models, for the second approach the baseline value was the average of CGM values from -24 to 00 h for the 00 to 24 h summary, the average of CGM values from 00 to 24 h for the 24 to 48 h summary, and the average of CGM values from 24 to 48 h for the 48 to 72 h summary.
  - Change from baseline in fasting glucose: The comparison of the effect of the 2 treatments on the change from baseline in fasting glucose MMTT (-15 minutes)

between Day -1 and Day 4 of Period 1 and Day -1 (Day 27) and Day 4 (Day 31) of Period 2 was performed in the same way as the primary endpoint analysis.

- Changes in AUC(0-4) in hormones, free fatty acids (FFAs), and C-peptide: The comparison of the effect of the 2 treatments on the changes in insulin, glucagon, glucagon-like peptide-1 (GLP-1), glucose-dependent insulin releasing polypeptide (GIP), FFAs, and C-peptide was performed in the same way as the primary endpoint analysis.
- MMTT-derived first phase insulin response: The comparison of the effect of the 2 treatments on the change in ΔI10/ΔG10 and ΔI30/ΔG30, between Days -1 and 4 was performed in the same way as the primary endpoint analysis.
- Homeostatic model assessment-insulin resistance (HOMA-IR) and homeostatic model assessment-insulin sensitivity (HOMA-S): A summary of HOMA-IR and HOMA-S at baseline and at Day 4, as well as change from baseline, was provided by treatment.
- 24-h urinary sodium (U-Na) and urinary potassium (U-K): The 24-h Na and K concentrations and their ratio (Na/K) in urine were analysed in the same way as the primary endpoint analysis.
- Tumour necrosis factor alpha (TNFα) concentrations: Descriptive statistics were tabulated for the individual measurement points of the lipopolysaccharide (LPS)-stimulated TNFα levels and area under the TNFα concentration versus time curve from zero to 24 h post-dose (AUC[0-24]). An analysis of variance model for AUC(0-24) with treatment, sequence, and subject as random effect was run separately for each cohort (Cohort 1 and Cohort 2) for the comparisons of the treatments at Day 3.
- PK data: The PK data were listed by cohort/patient and summarised by treatment for AZD9567 based on the PKAS. Descriptive statistics for calculated PK parameters included n, arithmetic mean, arithmetic SD, geometric mean, geometric mean – geometric standard deviation (gSD), geometric mean + gSD, geometric coefficient of variation %, median, minimum, and maximum values. For tmax, only median, minimum, and maximum values were presented.

- Safety endpoint analysis: Safety data were listed by cohort/patient and summarised by treatment based on the SAF, except for morning serum cortisol and adrenocorticotropic hormone (ACTH) data which were based on the FAS. The actual treatment was used for all safety and tolerability analyses. Safety was assessed by descriptive analysis of AEs/ serious adverse events (SAEs), vital signs, electrocardiograms (ECGs), and clinical laboratory assessments; the Medical Dictionary for Regulatory Activities version 24.0 was used to code AEs. Laboratory tests results (haematology, clinical chemistry, and urinalysis), ECG findings, and vital signs were summarised using appropriate descriptive statistics, including observed results and changes from baseline as appropriate. The

morning serum cortisol values and ACTH values were summarised using descriptive statistics and change from baseline was calculated.

- Two interim analyses were planned, conditional on the recruitment rate. Both interim analyses were conducted. The first interim analysis was conducted when 50% of the patients of Cohort 1 had completed the study. A second interim analysis was done after all patients in Cohort 1 had completed the study.

Study Population

- A total of 84 patients were enrolled at 3 CRUs in Germany. Of these, 46 (100.0%) patients were randomised to 1 of 2 sequence groups within 3 cohorts. Overall, of the patients who were randomised, 44 (95.7%) patients received at least 1 dose of study treatment, both in the first and second treatment period, and completed the study. Of the randomised patients, 2 patients did not receive study treatment in the first study period. There were 38 patients who failed screening (including 2 patients who also withdrew consent).
- In Cohort 1, there were 14 (100%) patients randomised to the 72 mg AZD9567/ 40 mg prednisolone group and 14 (100%) patients randomised to the 40 mg prednisolone/ 72 mg AZD9567 group. Of these, all except 1 patient in the 40 mg prednisolone/ 72 mg AZD9567 group received at least 1 dose of study treatment, both in the first and second treatment period, and completed the study.
- In Cohort 2, there were 5 (100%) patients randomised to the 40 mg AZD9567/ 20 mg prednisolone group and 4 (100%) patients randomised to the 20 mg prednisolone/40 mg AZD9567 group. Of these, all except 1 patient in the 20 mg prednisolone/40 mg AZD9567 group received at least 1 dose of study treatment, both in the first and second treatment period, and completed the study.
- In Cohort 3, there were 4 (100%) patients randomised to the placebo/5 mg prednisolone group and 5 (100%) patients randomised to the 5 mg prednisolone/placebo group. Of these, all patients received at least 1 dose of study treatment, both in the first and second treatment period, and completed the study.
- There were no imbalances between treatment groups within cohorts with regard to demographic and baseline characteristics, medical history, and prior and concomitant medications, that could have a potential influence on the results and their interpretation.
- The patient baseline characteristics, medical history, and prior and concomitant medications were typical of a population of patients with T2DM.
- The data cut-off for the analyses presented was 09 June 2021.

Summary of Efficacy Results

This study did not address the clinical efficacy of the IMPs (ie, anti-inflammatory effect).

Summary of Pharmacokinetic Results

- AZD9567 was rapidly absorbed with a median tmax of 0.50 h and remained quantifiable throughout the 0 to 30 h post-dose sampling interval.

- Following maximum observed drug concentration (Cmax) plasma concentrations of AZD9567 declined, generally in an essentially monophasic manner, with mean terminal elimination half-life (t½λz) values of 6.99 h and 6.16 h at the 72 mg and 40 mg dose levels, respectively.
- The exposure was approximately dose proportional between the 72 mg and 40 mg dose levels.
- The between-subject variability in area under the plasma concentration versus time curve from zero to 6 h post-dose (AUC[0-6]) and Cmax was moderate (25% to 40%) and high (> 40%) for area under the plasma concentration versus time curve from zero to 24 h post-dose (AUC[0-24]) and area under the plasma concentration versus time curve from zero to the last quantifiable concentration (AUClast).

Summary of Pharmacodynamic Results

In this study in patients with T2DM who received 72 mg AZD9567 and 40 mg prednisolone (Cohort 1) over two 72-h periods in a cross-over design, the following results were found:

- Following a standardised MMTT, there was a statistically significantly different effect on glucose homeostasis in the 72 mg AZD9567 group compared to the 40 mg prednisolone group, as indicated by a:
  - Larger decrease in glucose AUC(0-4) MMTT at Day 4 in the 72 mg AZD9567 group (LS mean difference: -132.9528 min*mmol/L [95% CI: -256.5082, -9.3973; p-value = 0.036]) (primary PD endpoint).
  - Increase in insulin AUC(0-4) MMTT at Day 4 in the 72 mg AZD9567 group compared to a decrease in the 40 mg prednisolone group (LS mean difference: 20498.7517 min*pmol/L [95% CI: 10819.2989, 30178.2044; p-value < 0.001]).
  - Decrease in glucagon AUC(0-4) MMTT at Day 4 in the 72 mg AZD9567 group compared to an increase in the 40 mg prednisolone group (LS mean difference: -1002.5864 min*pmol/L [95% CI: -1620.2150, -384.9577; p-value = 0.003]).
  - Smaller increase in GLP-1 AUC(0-4) MMTT at Day 4 in the 72 mg AZD9567 group (LS mean difference: -1225.9050 min*pmol/L [95% CI: -2007.2241, -444.5859; p-value = 0.004]).
  - Larger increase in C-peptide AUC(0-4) MMTT at Day 4 in the 72 mg AZD9567 group (LS mean difference: 60.4211 min*nmol/L [95% CI: 29.4904, 91.3518; p-value < 0.001]).
- There was a statistically significantly different effect on glucose homeostasis in the 72 mg AZD9567 group compared to the 40 mg prednisolone group, as indicated by a:
  - Lower mean glucose levels (measured by CGM) at 48 to 72 h in the 72 mg AZD9567 group (LS mean difference: -1.5067 mmol/L [95% CI: -2.0820, -0.9314; p-value < 0.001]).

  - Smaller increase in mean glucose levels (measured by CGM) in periods 00 to 24 h, 24 to 48 h, and 48 to 72 h in the 72 mg AZD9567 group according to mixed models approach 1 (period 00 to 24 h, LS mean difference: -1.5015 mmol/L [95% CI: -2.2258, -0.7773; p-value < 0.001]; period 24 to 48 h, LS mean difference: -1.8643 mmol/L [95% CI: -2.5611, -1.1674; p-value < 0.001], period 48 to 72 h, LS mean difference: -1.5998 mmol/L [95% CI: -2.3025, -0.8971; p-value < 0.001]).
  - Smaller increase in mean glucose levels (measured by CGM) in period 00 to 24 h in the 72 mg AZD9567 group according to mixed models approach 2 (LS mean difference: -1.5015 mmol/L [95% CI: -2.2258, -0.7773; p-value < 0.001]).
- There was no statistically significantly different effect on glucose homeostasis with regard to fasting glucose MMTT, GIP AUC(0-4) MMTT, and FFA AUC(0-4) MMTT at Day 4.
- There was no statistically significant difference on beta cell function with regard to MMTT-derived first phase insulin response (ΔI10/ΔG10, ΔI30/ΔG30, ΔC10/ΔG10, and ΔC30/ΔG30) at Day 4. Furthermore, there was no relevant difference in HOMA-IR and HOMA-S.
- There was no statistically significant difference on U-Na and U-K excretion at Day 3.
- There was no statistically significant difference in LPS-stimulated TNFα AUC(0-24) at Day 3, neither for the comparison of 72 mg AZD9567 versus 40 mg prednisolone nor for the comparison 40 mg AZD9567 versus 20 mg prednisolone. The data observed suggest a correlation between increasing AZD9567 concentration and inhibition of TNFα release.
- CCI [redacted]
- CCI [redacted]

CCI [redacted]

Summary of Safety Results

- Out of the 44 patients in the SAF, a total of 16 patients had at least 1 AE of any category in this study (10 [37.0%] patients in Cohort 1, 5 [62.5%] patients in Cohort 2, and 1 [11.1%] patient in Cohort 3). The following AEs were reported:
  - Cohort 1: Conjunctivitis, nasopharyngitis, pollakiuria, and fatigue (1 [3.7%] patient each) in patients on 72 mg AZD9567 treatment; cellulitis, hyperglycaemia, hypoglycaemia, dizziness, headache, administration site phlebitis, catheter site erythema, and mucosal inflammation (1 [3.7%] patient each) in patients on 40 mg prednisolone treatment.
  - Cohort 2: Headache and back pain (1 [12.5%] patient each) in patients on 40 mg AZD9567 treatment; headache (2 [25.0%] patients), dizziness, haematochezia,

catheter site related reaction, and blood pressure increased (1 [12.5%] patient each) in patients on 20 mg prednisolone treatment.

  - Cohort 3: Diarrhoea (1 [11.1%] patient) in a patient on placebo treatment. No AEs were reported in patients on 5 mg prednisolone treatment.

- No SAEs (including events with a fatal outcome), AEs leading to discontinuation of IMP, AEs leading to interruption of IMP, or AEs leading to withdrawal from the study were reported in any of the 3 cohorts. Two patients in Cohort 1 each had an SAE outside of the treatment period. One patient had the SAE of sarcoidosis which was considered severe in intensity. One patient had the SAE of humerus fracture which was considered moderate in intensity. Both SAEs were considered to be unrelated to the IMP by the Investigator.
- There were no clinically important trends or changes compared to baseline at Day 4 in haematology, clinical chemistry, and urinalysis parameters. There was a trend in potassium reduction that was greater for prednisolone treatment than for AZD9567 treatment, which is consistent with a greater mineralocorticoid effect of prednisolone.
- Mean morning serum cortisol values at Day 4 were decreased compared to baseline across the cohorts and in each treatment group.
- Mean ACTH values were lower on Day 4 compared to baseline across the cohorts and in each treatment group, except for patients on 5 mg prednisolone treatment in Cohort 3.
- There were no clinically important trends or changes at Day 4 compared to baseline in vital signs or ECG parameters.
- In Cohort 1, 1 patient on 72 mg AZD9567 treatment and 1 patient on 40 mg prednisolone treatment had a QT interval corrected for heart rate using Fridericia's formula (QTcF) value > 450 msec and 1 patient on 72 mg AZD9567 treatment had a QTcF increase of > 30 msec from baseline at any observation on treatment; in Cohort 3, 1 patient on placebo treatment had a QTcF value of > 450 msec and an increase of > 30 msec from baseline at any observation on treatment.

Conclusions

- The PD effect of AZD9567 on glucose homeostasis supports evidence that AZD9567 is a glucocorticoid receptor modulator with an improved dysglycaemic side effect profile and a favourable and differentiated metabolic profile with regard to key glycaemic hormones (insulin, glucagon) compared to prednisolone.
- Following 3 days of dosing, there was no statistically significant difference in the anti-inflammatory effect between the 72 mg AZD9567 group and the 40 mg prednisolone group as measured by ex-vivo stimulated TNFα AUC(0-24).
- Following rapid absorption with a median tmax of 0.50 h, plasma concentrations of AZD9567 declined in an essentially monophasic manner with mean t½λz values of 6.99 h and 6.16 h at the 72 mg and 40 mg dose levels, respectively.
- The safety and tolerability profile of AZD9567 was consistent with the known safety profile of the compound, established in previous studies. There was a trend in potassium reduction that was greater for prednisolone treatment than for AZD9567 treatment, which is consistent with a greater mineralocorticoid effect of prednisolone.