ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 11/22/2012

ClinicalTrials.gov ID: NCT01020123

Study Identification

Unique Protocol ID:	D1020C00009
Brief Title:	Evaluate Efficacy, Safety and Tolerability of AZD1656 as Add-on Treatment to Metformin in Type 2 Diabetes Mellitus (TD2M) Patients
Official Title:	A 4-month, Randomized, Double-blind, Placebo- and Active-Controlled, Multi-centre, Parallel-Group Study, With an Optional 2-month Extension, to Evaluate Efficacy, Safety and Tolerability of AZD1656 as Add-on Treatment to Metformin in Type 2 Diabetes Mellitus Patients
Secondary IDs:	

Study Status

Record Verification:	November 2012
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2011 [Actual]

Sponsor/Collaborators

Sponsor:	AstraZeneca
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 76.507 Serial Number: Has Expanded Access? No
Review Board:	Approval Status: Board Name: Board Affiliation: Phone: Email:
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Chile: Instituto de Salud Pública de Chile Germany: Federal Institute for Drugs and Medical Devices Hungary: National Institute of Pharmacy Latvia: State Agency of Medicines Lithuania: State Medicine Control Agency - Ministry of Health Mexico: Federal Commission for Protection Against Health Risks Peru: General Directorate of Pharmaceuticals, Devices, and Drugs Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products Romania: National Medicines Agency Sweden: Medical Products Agency United Kingdom: Medicines and Healthcare Products Regulatory Agency United States: Food and Drug Administration

Study Description

Brief Summary:	The primary aim is to evaluate Efficacy, Safety and Tolerability of AZD1656 as Add-on Treatment to Metformin in TD2M Patients
Detailed Description:	

Conditions

Conditions:	Type II Diabetes Mellitus

Keywords: Type II Diabetes Mellitus
metformin
glipizide

Study Design

Study Type: Interventional
Primary Purpose: Treatment
Study Phase: Phase 2
Intervention Model: Parallel Assignment
Number of Arms: 7
Masking: Double Blind (Subject, Investigator)
Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Enrollment: 530 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1 AZD1656	Drug: AZD1656 Different doses of AZD1656 administered to 5 groups of patients
Experimental: 2 AZD1656	Drug: AZD1656 Different doses of AZD1656 administered to 5 groups of patients
Experimental: 3 AZD1656	Drug: AZD1656 Different doses of AZD1656 administered to 5 groups of patients
Experimental: 4 AZD1656	Drug: AZD1656 Different doses of AZD1656 administered to 5 groups of patients
Experimental: 5 AZD1656	Drug: AZD1656 Different doses of AZD1656 administered to 5 groups of patients
Placebo Comparator: 6	Drug: Placebo AZD1656 placebo and glipizide placebo administered to 1 group of patients
Active Comparator: 7 Glipizide administered to 1 group of patients	Drug: Glipizide Glipizide administered to 1 group of patients

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- female of non-childbearing potential
- Treated with maximally tolerated dose of metformin (≥ 1500mg/day) for at least 10 weeks prior to enrolment.
- Patients with HbA1c ≥ 7.5 but ≤ 10% at enrolment visit (Visit 1) can enter cohort 1.Patients with HbA1c between >10 % and <12 % can enter the open-label arm with AZD1656 (cohort 2)

Exclusion Criteria:

- Significant cardiovascular event within the last 6 months prior to enrolment or heart failure New York Heart Association (NYHA) class III-IV.
- Impaired renal function in terms of GFR<60 ml/min, based on Modification of Diet in Renal Disease Study Group (MDRD) calculation.
- Use of warfarin or amiodarone within 3 months prior to enrolment (screening) and use of potent CYP450 inhibitors, eg, ketoconazole and/or macrolide antibiotics within 14 days before randomisation.

Contacts/Locations

Study Officials: Eva Johnsson
Study Director
AstraZeneca R&D Mölndal

John Wilding, DM FRCP
Study Principal Investigator
University Hospital Aintree

Locations: Chile
Research Site
Temuco, Novena Region, Chile

Research Site
Brentwood, TN, Chile

Research Site
Santiago, Chile

Research Site
Temuco, Chile

Germany
Research Site
Dresden, SN, Germany

Research Site
Brentwood, TN, Germany

Research Site
Aschaffenburg, Germany

Research Site
Berlin, Germany

Research Site
Bochum, Germany

Research Site
Dortmund, Germany

Research Site
Frankfurt, Germany

Research Site
Görlitz, Germany

Research Site
Hamburg, Germany

Research Site
Lubeck, Germany

Research Site
Magdeburg, Germany

United Kingdom
Research Site
Paignton, Devon, United Kingdom

Research Site
Liverpool, Merseyside, United Kingdom

Research Site
St. Laurent, QC, United Kingdom

Research Site
Cardiff, United Kingdom

Research Site
Chorley, United Kingdom

Research Site
Glasgow, United Kingdom

Research Site
Stevenage, United Kingdom

Research Site
West Bromwich, United Kingdom

Research Site
West Lothian, United Kingdom

Hungary
Research Site
St. Laurent, QC, Hungary

Research Site
Balatonfured, Hungary

Research Site
Bekescsaba, Hungary

Research Site
Dunaujvaros, Hungary

Research Site
Eger, Hungary

Research Site
Gyula, Hungary

Research Site
Kaposvar, Hungary

Research Site
Nyiregyhaza, Hungary

Research Site
Szekszard, Hungary

Research Site
Szigetvar, Hungary

Research Site
Zalaegerszeg, Hungary

Latvia
Research Site
Brentwood, TN, Latvia

Research Site
Daugavpils, Latvia

Research Site
Jekabpils, Latvia

Research Site
Jelgava, Latvia

Research Site
Limbazi, Latvia

Research Site
Riga, Latvia

Research Site
Talsi, Latvia

Research Site
Valmiera, Latvia

Lithuania
Research Site
Brentwood, TN, Lithuania

Research Site
Kaunas, Lithuania

Mexico
Research Site
Aguascalientes, Aguascalientes, Mexico

Research Site

Zapopan, Jalisco, Mexico

Research Site
Monterrey, Mexico, Mexico

Research Site
Cuernavaca, Morelos, Mexico

Research Site
Monterrey, Nuevo Leon, Mexico

Research Site
Brentwood, TN, Mexico

Research Site
Merida, Yucatan, Mexico

Research Site
Meridas, Yucatan, Mexico

Research Site
Chiuahua, Mexico

Research Site
San Luis Potosi, Mexico

Peru
Research Site
Lima, Lima, Peru

Research Site
Brentwood, TN, Peru

Research Site
Callao, Peru

Research Site
Lambayeque, Peru

Research Site
Lima, Peru

Research Site
Piura, Peru

Research Site

Trujillo, Peru

Poland
Research Site
Brentwood, TN, Poland

Research Site
Gdansk, Poland

Research Site
Krakow, Poland

Research Site
Kutno, Poland

Research Site
Wroclaw, Poland

Romania
Research Site
Alba Iulia, Alba, Romania

Research Site
Tg Mures, Mures, Romania

Research Site
Brentwood, TN, Romania

Research Site
Galati, Romania

Research Site
Ploiesti, Romania

Research Site
Sibiu, Romania

Research Site
Timisoara, Romania

Sweden
Research Site
Brentwood, TN, Sweden

Research Site
Huddinge, Sweden

Research Site
Lund, Sweden

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Main Period

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Started	93	91	52	40	88	94
Completed	76	77	44	33	77	83
Not Completed	17	14	8	7	11	11
Withdrawal by Subject	6	5	3	1	6	3
Eligibility Criteria not fullfilled	0	1	0	0	1	0

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Adverse Event	5	2	2	1	1	2
Protocol Violation	4	4	2	5	2	3
Lost to Follow-up	0	2	0	0	0	0
Unclasified	2	0	1	0	1	3

	Open Label
Started	72
Completed	61
Not Completed	11
Withdrawal by Subject	2
Eligibility Criteria not fullfilled	0
Adverse Event	1
Protocol Violation	2
Lost to Follow-up	0
Unclasified	6

Extention Period

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Started	40 [1]	35 [1]	19 [1]	13 [1]	31 [1]	38 [1]
Completed	37	33	17	12	31	36
Not Completed	3	2	2	1	0	2
Withdrawal by Subject	2	1	1	0	0	0
Adverse Event	0	0	0	1	0	0
Protocol Violation	1	1	1	0	0	0
Lost to Follow-up	0	0	0	0	0	2

[1] Not everyone accepted protocol amendment allowing to enter extension period or was asked to enter.

	Open Label
Started	19 [1]
Completed	18
Not Completed	1
Withdrawal by Subject	0
Adverse Event	0
Protocol Violation	1
Lost to Follow-up	0

[1] Not everyone accepted protocol amendment allowing to enter extension period or was asked to enter.

Baseline Characteristics

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Baseline Measures

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants	93	91	52	40	88	94
Age, Continuous [units: Year] Mean (Full Range)	57.1 (34 to 81)	57.1 (32 to 80)	54.4 (23 to 77)	57.4 (35 to 80)	56.9 (30 to 75)	57.1 (36 to 78)

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Gender, Male/Female [units: Participants]						
Female	47	46	22	19	45	46
Male	46	45	30	21	43	48

	Open Label
Number of Participants	72
Age, Continuous [units: Year] Mean (Full Range)	53.1 (20 to 69)
Gender, Male/Female [units: Participants]	
Female	37
Male	35

Outcome Measures

1. Primary Outcome Measure:

Measure Title	HbA1c: Change From Baseline to 4 Month
Measure Description	AZD1656 is analyzed in a ANCOVA model (Glipized and Open Label is Not Included in the model), FAS Prior to Rescue
Time Frame	Baseline to 4th Month
Safety Issue?	No

Analysis Population Description

The population is FAS prior to rescue, using the LOCF values (see table 27 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose

	Description
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	80	82	47	34	82
HbA1c: Change From Baseline to 4 Month [units: Percentage] Mean (95% Confidence Interval)	-1.25 (-1.49 to -1.01)	-1.26 (-1.49 to -1.02)	-0.67 (-0.99 to -0.36)	-0.61 (-0.98 to -0.24)	-0.45 (-0.69 to -0.21)

2. Secondary Outcome Measure:

Measure Title	FPG: to Evaluate Change From Baseline to 4 Month, Compared With Placebo, FAS Prior to Rescue.
Measure Description	AZD1656 is analyzed in a ANCOVA model (Glipized and Open Label is Not Included in the model), FAS Prior to Rescue.
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is FAS prior to rescue, using the LOCF values (see table 29 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	90	87	49	39	85
FPG: to Evaluate Change From Baseline to 4 Month, Compared With Placebo, FAS Prior to Rescue. [units: mmol/L] Mean (95% Confidence Interval)	-0.818 (-1.331 to -0.304)	-1.08 (-1.603 to -0.558)	0.041 (-0.656 to 0.738)	0.024 (-0.757 to 0.804)	-0.182 (-0.71 to 0.347)

3. Secondary Outcome Measure:

Measure Title	SMPG: Change From Baseline to 4 Month, Compared With Placebo, FAS Prior to Rescue.
Measure Description	AZD1656 is analyzed in a ANCOVA model (Glipized and Open Label is Not Included in the model), FAS Prior to Rescue.
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is FAS prior to rescue, using the LOCF values (see table 31 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	58	63	38	26	57
SMPG: Change From Baseline to 4 Month, Compared With Placebo, FAS Prior to Rescue. [units: mmol/L]	-1.596 (-2.176 to -1.016)	-1.557 (-2.117 to -0.997)	-0.874 (-1.591 to -0.157)	-0.604 (-1.472 to 0.265)	-0.213 (-0.799 to 0.372)

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Mean (95% Confidence Interval)					

4. Secondary Outcome Measure:

Measure Title	OGTT/Plasma Glucose
Measure Description	The relative change in AUC
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is FAS prior to rescue, using the LOCF values (see table 142 in CSR)The first 50% of patients enrolled in the study were supposed to undertake OGTT, actual number participating was 52%. However, more than 60% of the OGTT patients were excluded from the analyses, as their measurements did not comply with the protocol

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	17	13	7	8	17
OGTT/Plasma Glucose [units: ratio] Geometric Mean (95% Confidence Interval)	0.92 (0.82 to 1.02)	0.84 (0.75 to 0.96)	1.02 (0.86 to 1.22)	0.99 (0.84 to 1.16)	0.99 (0.88 to 1.10)

5. Secondary Outcome Measure:

Measure Title	OGTT/Insulin
Measure Description	The Relative Change in AUC FAS Prior to Rescue
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is FAS prior to rescue, using the LOCF values (see table 146 in CSR)The first 50% of patients enrolled in the study were supposed to undertake OGTT, actual number participating was 52%. However, more than 60% of the OGTT patients were excluded from the analyses, as their measurements did not comply with the protocol

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	16	12	6	10	16
OGTT/Insulin [units: ratio] Geometric Mean (95% Confidence Interval)	0.81 (0.66 to 0.99)	1.08 (0.85 to 1.36)	0.97 (0.69 to 1.35)	0.90 (0.69 to 1.16)	0.91 (0.74 to 1.12)

6. Secondary Outcome Measure:

Measure Title	OGTT/C-peptide
Measure Description	The relative change, FAS prior to rescue
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is FAS prior to rescue, using the LOCF values (see table 150 in CSR)The first 50% of patients enrolled in the study were supposed to undertake OGTT, actual number participating was 52%. However, more than 60% of the OGTT patients were excluded from the analyses, as their measurements did not comply with the protocol

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	17	13	7	10	16
OGTT/C-peptide [units: ratio] Geometric Mean (95% Confidence Interval)	0.97 (0.85 to 1.10)	1.11 (0.96 to 1.29)	0.90 (0.74 to 1.10)	0.95 (0.81 to 1.13)	1.00 (0.87 to 1.14)

7. Secondary Outcome Measure:

Measure Title	OGTT/Pro-insulin/Insulin
Measure Description	The relative change, FAS prior to rescue
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is FAS prior to rescue, using the LOCF values (see table 154 in CSR)The first 50% of patients enrolled in the study were supposed to undertake OGTT, actual number participating was 52%. However, more than 60% of the OGTT patients were excluded from the analyses, as their measurements did not comply with the protocol

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	16	12	6	10	14
OGTT/Pro-insulin/Insulin [units: Ratio] Geometric Mean (95% Confidence Interval)	1.496 (1.250 to 1.791)	1.199 (0.973 to 1.476)	1.248 (0.932 to 1.672)	1.431 (1.135 to 1.805)	1.185 (0.979 to 1.436)

8. Secondary Outcome Measure:

Measure Title	HbA1c ≤ 7
Measure Description	Number of responders ≤ 7, FAS prior to rescue.
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is FAS prior to rescue, using the observed cases (see table 35 in CSR).

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

	Description
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	74	73	38	32	69	78
HbA1c ≤ 7 [units: Participants]	43	43	14	11	16	50

	Open Label
Number of Participants Analyzed	48
HbA1c ≤ 7 [units: Participants]	24

9. Secondary Outcome Measure:

Measure Title	HbA1c ≤ 6.5
Measure Description	Number of Responders ≤ 6.5, FAS Prior to Rescue
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 228 in CSR).

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose

	Description
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	74	73	38	32	69	78
HbA1c ≤ 6.5 [units: Participants]	35	27	9	4	9	30

	Open Label
Number of Participants Analyzed	48
HbA1c ≤ 6.5 [units: Participants]	16

10. Secondary Outcome Measure:

Measure Title	LDL-C: Mean Ratio
Measure Description	Geometric mean ratio (safety analysis set, regardless of rescue) and a 95 % CI.
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 228 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose

	Description
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	74	75	43	33	73
LDL-C: Mean Ratio [units: ratio] Geometric Mean (95% Confidence Interval)	1.07 (1.01 to 1.13)	1.02 (0.97 to 1.08)	1.07 (0.99 to 1.15)	1.04 (0.96 to 1.13)	1.02 (0.97 to 1.08)

11. Secondary Outcome Measure:

Measure Title	HDL-C: Change From Baseline
Measure Description	Geometric mean ratio (safety analysis set, regardless of rescue) and a 95 % CI.
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 230 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	75	76	43	33	74
HDL-C: Change From Baseline [units: ratio] Geometric Mean (95% Confidence Interval)	1.06 (1.02 to 1.09)	1.06 (1.03 to 1.10)	1.05 (1.01 to 1.09)	1.03 (0.99 to 1.08)	1.03 (1.00 to 1.06)

12. Secondary Outcome Measure:

Measure Title	Total Cholesterol: Change From Baseline
Measure Description	Geometric mean ratio (safety analysis set, regardless of rescue) and a 95 % CI.
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 232 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	75	76	43	33	74
Total Cholesterol: Change From Baseline [units: ratio] Geometric Mean (95% Confidence Interval)	1.09 (1.04 to 1.13)	1.08 (1.04 to 1.12)	1.07 (1.02 to 1.13)	1.04 (0.98 to 1.10)	1.03 (0.99 to 1.07)

13. Secondary Outcome Measure:

Measure Title	Triglycerides: Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 226 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	75	43	33	74	82
Triglycerides: Change From Baseline [units: mg/dL] Mean (Standard Deviation)	40.9 (115.3)	38.7 (99.3)	19.8 (185.3)	4.4 (49.3)	13.7 (139.4)	18.7 (152.8)

	Open Label
Number of Participants Analyzed	58
Triglycerides: Change From Baseline [units: mg/dL]	29.8 (174.3)

	Open Label
Mean (Standard Deviation)	

14. Secondary Outcome Measure:

Measure Title	C-reactive Protein: Change From Baseline
Measure Description	Geometric mean ratio (safety analysis set, regardless of rescue) and a 95 % CI
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 234 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo
Number of Participants Analyzed	75	76	43	33	75
C-reactive Protein: Change From Baseline [units: ratio] Geometric Mean (95% Confidence Interval)	0.30 (0.08 to 0.52)	0.08 (-0.14 to 0.30)	0.09 (-0.20 to 0.30)	0.06 (-0.40 to 0.27)	-0.02 (-0.24 to 0.20)

15. Secondary Outcome Measure:

Measure Title	Systolic Blood Pressure, Change From Baseline
Measure Description	Summary statistic of change from baseline

Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 237 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	73	38	32	69	79
Systolic Blood Pressure, Change From Baseline [units: mmHg] Mean (Standard Deviation)	-0.4 (12.6)	0.4 (9.9)	5.7 (11.3)	0.1 (12.6)	-0.2 (13.7)	-1.1 (13.5)

	Open Label
Number of Participants Analyzed	58
Systolic Blood Pressure, Change From Baseline [units: mmHg] Mean (Standard Deviation)	-0.3 (11.7)

16. Secondary Outcome Measure:

Measure Title	Diastolic Blood Pressure, Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 240 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	73	38	32	69	79
Diastolic Blood Pressure, Change From Baseline [units: mmHg] Mean (Standard Deviation)	1.1 (8.6)	1.4 (8.5)	1.3 (9.1)	-0.9 (10.8)	-0.3 (8.5)	-0.1 (7.2)

	Open Label
Number of Participants Analyzed	58
Diastolic Blood Pressure, Change From Baseline [units: mmHg] Mean (Standard Deviation)	0.5 (7.7)

17. Secondary Outcome Measure:

Measure Title	Pulse, Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 236 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	73	38	32	69	79
Pulse, Change From Baseline [units: Beats/min] Mean (Standard Deviation)	0.4 (8.8)	1.6 (7.9)	1.3 (7.9)	0.3 (9.1)	-1.1 (9.4)	-0.4 (11.6)

	Open Label
Number of Participants Analyzed	58
Pulse, Change From Baseline [units: Beats/min]	1.3 (8.5)

	Open Label
Mean (Standard Deviation)	

18. Secondary Outcome Measure:

Measure Title	Weight, Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 244 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	73	38	32	69	79
Weight, Change From Baseline [units: kg] Mean (Standard Deviation)	-0.3 (2.5)	-0.6 (2.9)	-1.2 (2.7)	-1.4 (2.3)	-1.0 (2.5)	1.0 (3.4)

	Open Label
Number of Participants Analyzed	48
Weight, Change From Baseline [units: kg] Mean (Standard Deviation)	-0.4 (4.4)

19. Secondary Outcome Measure:

Measure Title	QTcF; Electorcardiagram Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 258 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	74	76	43	34	77	83
QTcF; Electorcardiagram Change From Baseline [units: msec] Mean (Standard Deviation)	4.4 (15.6)	4.0 (14.5)	-2.6 (12.6)	3.8 (17.9)	2.2 (13.8)	2.7 (21.5)

	Open Label
Number of Participants Analyzed	63
QTcF; Electorcardiagram Change From Baseline [units: msec] Mean (Standard Deviation)	1.6 (16.4)

20. Secondary Outcome Measure:

Measure Title	Haemoglobin; Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

population is safety analysis set regardless of rescue, using the observed cases (see table 197 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	76	77	44	32	76	83
Haemoglobin; Change From Baseline [units: g/dL]	-0.20 (0.68)	-0.18 (0.62)	0.00 (0.63)	-0.11 (0.69)	-0.20 (0.71)	0.02 (0.69)

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Mean (Standard Deviation)						

	Open Label
Number of Participants Analyzed	61
Haemoglobin; Change From Baseline [units: g/dL] Mean (Standard Deviation)	-0.25 (0.76)

21. Secondary Outcome Measure:

Measure Title	Leukocytes; Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 198 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	76	77	44	32	76	83
Leukocytes; Change From Baseline [units: *10^3 cells/µL] Mean (Standard Deviation)	0.39 (1.29)	0.34 (1.59)	0.35 (1.41)	-0.15 (1.09)	-0.8 (1.09)	0.27 (1.43)

	Open Label
Number of Participants Analyzed	61
Leukocytes; Change From Baseline [units: *10^3 cells/µL] Mean (Standard Deviation)	-40 (1.31)

22. Secondary Outcome Measure:

Measure Title	Sodium; Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 215 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose

	Description
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	77	44	33	76	83
Sodium; Change From Baseline [units: mEq/L] Mean (Standard Deviation)	-0.6 (2.4)	-0.7 (2.4)	-0.4 (3.0)	-0.1 (2.6)	0.0 (2.6)	-0.6 (3.3)

	Open Label
Number of Participants Analyzed	60
Sodium; Change From Baseline [units: mEq/L] Mean (Standard Deviation)	0.5 (2.6)

23. Secondary Outcome Measure:

Measure Title	Potassium; Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 214 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose

	Description
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	77	43	32	75	82
Potassium; Change From Baseline [units: mEq/L] Mean (Standard Deviation)	0.02 (0.45)	-0.02 (0.26)	0.00 (0.35)	-0.01 (0.29)	-0.02 (0.34)	0.07 (0.39)

	Open Label
Number of Participants Analyzed	58
Potassium; Change From Baseline [units: mEq/L] Mean (Standard Deviation)	0.05 (0.38)

24. Secondary Outcome Measure:

Measure Title	Creatinine; Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 211 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	77	43	32	75	82
Creatinine; Change From Baseline [units: IU/L] Mean (Standard Deviation)	0.4 (70.5)	-9.9 (87.8)	8.5 (88.7)	-8.3 (39.1)	-0.1 (32.2)	15.9 (67.1)

	Open Label
Number of Participants Analyzed	59
Creatinine; Change From Baseline [units: IU/L] Mean (Standard Deviation)	-7.3 (47)

25. Secondary Outcome Measure:

Measure Title	ALT; Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 206 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	76	43	32	75	82
ALT; Change From Baseline [units: IU/L] Mean (Standard Deviation)	2.0 (12.0)	1.7 (14.8)	3.2 (17.7)	-1.8 (-1.8)	-0.4 (11.3)	2.0 (15.3)

	Open Label
Number of Participants Analyzed	59
ALT; Change From Baseline [units: IU/L] Mean (Standard Deviation)	-0.4 (15.5)

26. Secondary Outcome Measure:

Measure Title	AST; Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month

Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 207 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	76	43	32	75	82
AST; Change From Baseline [units: IU/L] Mean (Standard Deviation)	2.4 (9.8)	2.0 (11.0)	2.8 (13.1)	-0.6 (8.9)	-0.1 (7.9)	2.1 (13.3)

	Open Label
Number of Participants Analyzed	59
AST; Change From Baseline [units: IU/L] Mean (Standard Deviation)	2.7 (9.6)

27. Secondary Outcome Measure:

Measure Title	Alkaline Phosphatase; Change From Baseline

Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 208 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	77	44	33	76	83
Alkaline Phosphatase; Change From Baseline [units: IU/L] Mean (Standard Deviation)	3.8 (17.5)	-1.3 (13.3)	0.0 (13.6)	-1.8 (11.9)	-3.4 (11.5)	-4.2 (16.7)

	Open Label
Number of Participants Analyzed	59
Alkaline Phosphatase; Change From Baseline [units: IU/L] Mean (Standard Deviation)	-11.7 (24.7)

28. Secondary Outcome Measure:

Measure Title	Bilirubin; Change From Baseline
Measure Description	Summary statistic of change from baseline
Time Frame	baseline to 4 month
Safety Issue?	No

Analysis Population Description

The population is safety analysis set regardless of rescue, using the observed cases (see table 209 in CSR)

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Placebo	Glipizide
Number of Participants Analyzed	75	77	44	33	76	83
Bilirubin; Change From Baseline [units: mg/dL] Mean (Standard Deviation)	-0.02 (0.17)	-0.06 (0.21)	0.02 (0.13)	-0.05 (0.20)	-0.01 (0.20)	-0.07 (0.20)

	Open Label
Number of Participants Analyzed	59
Bilirubin; Change From Baseline [units: mg/dL] Mean (Standard Deviation)	-11.7 (24.7)

29. Secondary Outcome Measure:

Measure Title	CL/F to Characterise the PK Properties of AZD1656.
Measure Description	The value is calculated using an allometric model (of a patient weighting 75 kg). The value is independent treatment given.
Time Frame	at 4 month
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Open Label
Number of Participants Analyzed	86	87	49	39	70
CL/F to Characterise the PK Properties of AZD1656. [units: L/h] Mean (Standard Error)	9.29 (3.7)	9.29 (3.7)	9.29 (3.7)	9.29 (3.7)	9.29 (3.7)

30. Secondary Outcome Measure:

Measure Title	EC50 to Characterise the PD Properties of AZD1656.
Measure Description	The value is model based. The value is independent treatment given.
Time Frame	at 4 month

Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Measured Values

	Higher Dose	Lower Dose	40 mg Fixed Dose	20 mg Fixed Dose	Open Label
Number of Participants Analyzed	86	87	49	39	70
EC50 to Characterise the PD Properties of AZD1656. [units: nmol/L] Mean (Standard Error)	60.2 (14)	60.2 (14)	60.1 (14)	60.2 (14)	60.2 (14)

Reported Adverse Events

Time Frame	Baseline - 6 month
Additional Description	Safety was collected in 6 month

Reporting Groups

	Description
Higher Dose	20-200 mg AZD1656 add on to metformin, titrated dose
Lower Dose	10-140 mg AZD1656 add on to metformin, titrated dose
40 mg Fixed Dose	40 mg AZD1656 add on to metformin, fixed dose

	Description
20 mg Fixed Dose	20 mg AZD1656 add on to metformin, fixed dose
Placebo	Placebo add on to metformin
Glipizide	5-20 mg Glipizide add on to metformin, titrated dose
Open Label	Open label, 20-200 mg AZD1656 add on to metformin, titrated dose

Serious Adverse Events

	Higher Dose		Lower Dose		40 mg Fixed Dose		20 mg Fixed Dose		Placebo		Glipizide	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	2/92 (2.17%)		1/90 (1.11%)		1/50 (2%)		1/40 (2.5%)		2/87 (2.3%)		3/93 (3.23%)	
Cardiac disorders												
Acute myocardial infarction [A] †	0/92 (0%)	0	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	0/87 (0%)	0	1/93 (1.08%)	1
Angina Unstable [A] *	0/92 (0%)	0	0/90 (0%)	0	0/50 (0%)	0	1/40 (2.5%)	1	0/87 (0%)	0	0/93 (0%)	0
Angina pectoris [A] *	0/92 (0%)	0	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	0/87 (0%)	0	1/93 (1.08%)	1
Gastrointestinal disorders												
Diverticulum intestinal haemorrhagic [A] *	0/92 (0%)	0	0/90 (0%)	0	1/50 (2%)	1	0/40 (0%)	0	0/87 (0%)	0	0/93 (0%)	0
Infections and infestations												
Anal abscess [A] *	0/92 (0%)	0	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	0/87 (0%)	0	0/93 (0%)	0
Injury, poisoning and procedural complications												
Subdural haematoma [A] *	0/92 (0%)	0	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	1/87 (1.15%)	1	0/93 (0%)	0
Investigations												
Blood Creatine Phosphokinase Increased [A] *	1/92 (1.09%)	1	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	0/87 (0%)	0	0/93 (0%)	0

	Higher Dose		Lower Dose		40 mg Fixed Dose		20 mg Fixed Dose		Placebo		Glipizide	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Metabolism and nutrition disorders												
Diabetic foot [A] *	0/92 (0%)	0	1/90 (1.11%)	1	0/50 (0%)	0	0/40 (0%)	0	0/87 (0%)	0	0/93 (0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Brain neoplasm [A] *	0/92 (0%)	0	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	0/87 (0%)	0	1/93 (1.08%)	1
Nervous system disorders												
Cerebrovascular accident [A] *	1/92 (1.09%)	1	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	0/87 (0%)	0	0/93 (0%)	0
Renal and urinary disorders												
Renal failur acute [A] *	0/92 (0%)	0	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	1/87 (1.15%)	1	0/93 (0%)	0
Vascular disorders												
Hypertensive emergency [A] *	1/92 (1.09%)	1	0/90 (0%)	0	0/50 (0%)	0	0/40 (0%)	0	0/87 (0%)	0	0/93 (0%)	1

† Indicates events were collected by systematic assessment.
* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 10.0

	Open Label	
	Affected/At Risk (%)	# Events
Total	1/71 (1.41%)	
Cardiac disorders		
Acute myocardial infarction [A] †	0/71 (0%)	0
Angina Unstable [A] *	0/71 (0%)	0
Angina pectoris [A] *	0/71 (0%)	0
Gastrointestinal disorders		

	Open Label	
	Affected/At Risk (%)	# Events
Diverticulum intestinal haemorrhagic [A] *	0/71 (0%)	0
Infections and infestations		
Anal abscess [A] *	1/71 (1.41%)	1
Injury, poisoning and procedural complications		
Subdural haematoma [A] *	0/71 (0%)	0
Investigations		
Blood Creatine Phosphokinase Increased [A] *	0/71 (0%)	0
Metabolism and nutrition disorders		
Diabetic foot [A] *	0/71 (0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Brain neoplasm [A] *	0/71 (0%)	0
Nervous system disorders		
Cerebrovascular accident [A] *	0/71 (0%)	0
Renal and urinary disorders		
Renal failur acute [A] *	0/71 (0%)	0
Vascular disorders		
Hypertensive emergency [A] *	0/71 (0%)	0

† Indicates events were collected by systematic assessment.
* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 10.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Higher Dose		Lower Dose		40 mg Fixed Dose		20 mg Fixed Dose		Placebo		Glipizide	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	22/92 (23.91%)		36/90 (40%)		20/50 (40%)		10/40 (25%)		14/87 (16.09%)		35/93 (37.63%)	
Gastrointestinal disorders												
Diarrhoea A [1] *	4/92 (4.35%)		7/90 (7.78%)		3/50 (6%)		3/40 (7.5%)		3/87 (3.45%)		3/93 (3.23%)	
Gastritis A [1] *	1/92 (1.09%)		1/90 (1.11%)		1/50 (2%)		2/40 (5%)		0/87 (0%)		2/93 (2.15%)	
Nausea A [1] *	2/92 (2.17%)		2/90 (2.22%)		4/50 (8%)		0/40 (0%)		1/87 (1.15%)		1/93 (1.08%)	
Vomiting A [1] *	0/92 (0%)		2/90 (2.22%)		5/50 (10%)		0/40 (0%)		0/87 (0%)		1/93 (1.08%)	
General disorders												
Asthenia A [1] *	2/92 (2.17%)		4/90 (4.44%)		1/50 (2%)		0/40 (0%)		0/87 (0%)		7/93 (7.53%)	
Infections and infestations												
Gastroenteritis A [1] *	2/92 (2.17%)		0/90 (0%)		0/50 (0%)		2/40 (5%)		2/87 (2.3%)		0/93 (0%)	
Nasopharyngitis A [1] *	4/92 (4.35%)		9/90 (10%)		2/50 (4%)		1/40 (2.5%)		6/87 (6.9%)		3/93 (3.23%)	
Nervous system disorders												
Dizziness A [1] *	2/92 (2.17%)		3/90 (3.33%)		2/50 (4%)		0/40 (0%)		2/87 (2.3%)		6/93 (6.45%)	
Tremor A [1] *	4/92 (4.35%)		4/90 (4.44%)		1/50 (2%)		1/40 (2.5%)		0/87 (0%)		10/93 (10.75%)	
Skin and subcutaneous tissue disorders												
Hyperhidrosis A [1] *	1/92 (1.09%)		4/90 (4.44%)		1/50 (2%)		1/40 (2.5%)		0/87 (0%)		10/93 (10.75%)	

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (10.0)

[1] This iformation is based on tables 182 and 183 in the CSR

	Open Label	
	Affected/At Risk (%)	# Events
Total	9/71 (12.68%)	
Gastrointestinal disorders		
Diarrhoea A [1] *	0/71 (0%)	
Gastritis A [1] *	0/71 (0%)	
Nausea A [1] *	1/71 (1.41%)	
Vomiting A [1] *	0/71 (0%)	
General disorders		
Asthenia A [1] *	0/71 (0%)	
Infections and infestations		
Gastroenteritis A [1] *	0/71 (0%)	
Nasopharyngitis A [1] *	3/71 (4.23%)	
Nervous system disorders		
Dizziness A [1] *	2/71 (2.82%)	
Tremor A [1] *	1/71 (1.41%)	
Skin and subcutaneous tissue disorders		
Hyperhidrosis A [1] *	2/71 (2.82%)	

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.0)

[1] This iformation is based on tables 182 and 183 in the CSR

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

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