Clinical trial results:
A Phase II, randomised, double-blind, placebo-controlled clinical trial to assess the safety and efficacy of AZD1656 in diabetic patients hospitalised with suspected or confirmed COVID-19. The ARCADIA Trial

Summary

EudraCT number	2020-002211-21
Trial protocol	GB CZ RO
Global end of trial date	12 May 2021

Results information

Result version number	v1 (current)
This version publication date	12 February 2022
First version publication date	12 February 2022

Trial information

Trial identification

Sponsor protocol code	SGS.1656.201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04516759
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	St George Street Capital
Sponsor organisation address	2a/2b Thrales End Business Centre, Thrales End Lane , Harpenden, United Kingdom, AL5 3NS
Public contact	Clinical Trials, St George Street Capital Ltd, +44 7901119230, info@sgscapital.org
Scientific contact	Clinical Trials, St George Street Capital Ltd, +44 7901119230, info@sgscapital.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2021
Global end of trial reached?	Yes
Global end of trial date	12 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of AZD1656 on the cardiorespiratory complications of COVID-19 in hospitalised diabetic patients with known or suspected COVID-19 disease, as measured using the WHO 8-point Ordinal Scale for Clinical Improvement compared to placebo.

Protection of trial subjects:

The investigator or one of their associates informed the patients of the risks and benefits of the study. The patients were informed that they could withdraw from the study at any time for any reason. Consent was obtained in writing prior to any study-related activities; the investigator retained the ICFs, which were available to the Sponsor for inspection, and a copy of the signed consent form was provided to the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	United Kingdom: 71
Country: Number of subjects enrolled	Czechia: 49
Worldwide total number of subjects	153
EEA total number of subjects	82

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	69

From 65 to 84 years	82
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

It is noted that 3 more subjects were randomised, however, these subjects were never exposed to study drug and have not been included in this record.

Pre-assignment

Screening details:

Patients underwent a Screening Visit (V1) and Randomisation Visit (V2) to evaluate their eligibility to participate in the study and to commence study treatment (Day 1).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients receiving standard care plus placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 2 x tablets twice a day with food.

Arm title	AZD1656

Arm description:

Patients receiving standard of care plus AZD1656.

Arm type	Experimental
Investigational medicinal product name	AZD1656
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 2 x 50 mg tablets twice a day with food.

Number of subjects in period 1	Placebo	AZD1656
Started	73	80
Completed	61	70
Not completed	12	10
Consent withdrawn by subject	1	-
Reason not stated	11	10

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients receiving standard care plus placebo	
Reporting group title	AZD1656
Reporting group description:	
Patients receiving standard of care plus AZD1656.	

Reporting group values	Placebo	AZD1656	Total
Number of subjects	73	80	153
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	38	69
From 65-84 years	41	41	82
85 years and over	1	1	2
Gender categorical Units: Subjects			
Female	26	30	56
Male	47	50	97

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients receiving standard care plus placebo	
Reporting group title	AZD1656
Reporting group description:	
Patients receiving standard of care plus AZD1656.	

Primary: Clinical improvement at Day 14	
End point title	Clinical improvement at Day 14
End point description:	
Number of patients with clinical improvement based on categories 1-3 of the WHO OSCI rating at Day 14.	
End point type	Primary
End point timeframe:	
Assessment at Day 14	

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	80		
Units: Number of patients				
Treatment responder	51	61		
Treatment failure	21	18		
Missing	1	1		

Statistical analyses

Statistical analysis title	Comparison of AZD1656 vs placebo
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1854
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.32

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, including SAEs, were captured after signing the informed consent and until 7 days after treatment discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients receiving standard care plus placebo

Reporting group title	AZD1656

Reporting group description:

Patients receiving standard of care plus AZD1656.

Serious adverse events	Placebo	AZD1656	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 69 (20.29%)	8 / 84 (9.52%)	
number of deaths (all causes)	9	4	
number of deaths resulting from adverse events	9	4	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 69 (2.90%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			

subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	5 / 69 (7.25%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 2	
COVID-19 pneumonia			
subjects affected / exposed	2 / 69 (2.90%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	AZD1656	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 69 (18.84%)	28 / 84 (33.33%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Blood glucose decreased			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 69 (0.00%)	2 / 84 (2.38%)	
occurrences (all)	0	2	
Atrial flutter			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Reversible ischaemic neurological deficit			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 69 (2.90%)	0 / 84 (0.00%)	
occurrences (all)	2	0	
Leukocytosis			

subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Neutrophilia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 69 (0.00%)	2 / 84 (2.38%)	
occurrences (all)	0	2	
Abdominal tenderness			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 69 (4.35%)	4 / 84 (4.76%)	
occurrences (all)	3	4	
Hiccups			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Psychiatric disorders			
Restlessness			

subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	1 / 69 (1.45%)	1 / 84 (1.19%)	
occurrences (all)	1	1	
Sepsis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Device related infection			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Oral fungal infection			
subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			

subjects affected / exposed	0 / 69 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 69 (1.45%)	8 / 84 (9.52%)	
occurrences (all)	1	13	
Hyperglycaemia			
subjects affected / exposed	1 / 69 (1.45%)	4 / 84 (4.76%)	
occurrences (all)	1	4	
Hypokalaemia			
subjects affected / exposed	0 / 69 (0.00%)	4 / 84 (4.76%)	
occurrences (all)	0	4	
Hyperkalaemia			
subjects affected / exposed	0 / 69 (0.00%)	2 / 84 (2.38%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2020	Amendment 1, Version 1.1 (Czech Republic) - Modification of inclusion criteria: > Patients must be aged between 18 and 75 years inclusive. Patients older than 75 years were not eligible in contrast to the UK and Romania. > Patients must have confirmed COVID-19 at enrolment or within 48 hours of screening. Patients with suspected COVID-19 were not eligible in contrast to the UK and Romania. - Addition of an assessment of the clinical condition of all the patients 28 days (+/- 2 days) following the completion of study treatment as an onsite visit for patients still hospitalised or as a phone call for discharged patients. - Additional requirements for glycaemic control added. - Additional details on SARS-CoV-2 PCR testing for eligibility added
17 December 2020	Amendment 2, Version 1.2 (Romania) - A serum pregnancy test was added as requirement at baseline. - Additional requirements for glycaemic control added.
21 December 2020	Amendment 3, Version 2.0 (Global) -Clarified that treatment was to be administered for a maximum of 21 days. - Clarified that only out of range and clinically significant data of repeated ECG, clinical laboratory, cardiac biomarker, and SARS-CoV-2 PCR testing were to be recorded. It is noted that protocol version 2.0, identified as 'global', was only submitted in the UK and did not contain the local changes implemented in versions 1.1 and 1.2. Changes in version 2.0 were implemented in the applicable local versions 2.1 and 2.2.
13 January 2021	Amendment 4, Version 2.1 (Czech Republic) - Clarified that treatment was to be administered for a maximum of 21 days. - Clarified that only out of range and clinically significant data of repeated ECG, clinical laboratory, cardiac biomarker, and SARS-CoV-2 PCR testing were to be recorded.
13 January 2021	Amendment 5, Version 2.2 (Romania) - Clarified that treatment was to be administered for a maximum of 21 days. - Clarified that only out of range and clinically significant data of repeated ECG, clinical laboratory, cardiac biomarker, and SARS-CoV-2 PCR testing were to be recorded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

It is noted that per protocol, progression of disease (COVID-19) was not required to be reported as an adverse event. However all sites reported fatalities due to COVID-19 as AEs and these have been included in the SAEs presented here.

Notes: